

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202872Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 25, 2012
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	202872
Supplement#	
Applicant	Bausch and Lomb
Date of Submissions	November 29, 2011
PDUFA Goal Date	September 29, 2012
Proprietary Name / Established (USAN) names	Lotemax (loteprednol etabonate ophthalmic gel) 0.5%
Dosage forms / Strength	Topical ophthalmic gel 0.5%
Proposed Indication(s)	Treatment of post-operative inflammation and pain following ocular surgery
Recommended:	Recommended for Approval

1. Introduction

Loteprednol etabonate (LE) is a corticosteroid that Bausch & Lomb originally developed as a topical ophthalmic suspension 0.5% (Lotemax). Lotemax is approved for the treatment of steroid responsive inflammatory conditions ocular inflammatory disorders when the inherent hazard of steroid use is accepted to obtain an advisable diminution of edema and inflammation and treatment of postoperative inflammation following ocular surgery. Alrex (loteprednol etabonate ophthalmic suspension) 0.2% is approved for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis. A fixed combination product consisting of LE 0.5%/tobramycin 0.3% ophthalmic suspension (Zylet) is approved for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. LE ointment 0.5% (Lotemax) is approved for the treatment of post-operative inflammation and pain following ocular surgery.

The current application is for a new formulation, LE ophthalmic gel 0.5% (LE Gel) for the treatment of post-operative inflammation and pain following ocular surgery. The objective of a gel formulation was to provide an alternative ophthalmic delivery dosage form for patients requiring treatment for inflammation and pain following ocular surgery.

2. Background

The product development for loteprednol etabonate ophthalmic gel, 0.5% was conducted under IND 102,654. There was a PIND meeting on August 4, 2008, End-of-Phase 2 meeting on August 26, 2009, and Pre-NDA meeting on April 29, 2011.

SPA-1 for protocol #576 and SPA-2 for protocol #577 received Special Protocol – No Agreement letters on 1/15/2009. The Division provided comments in the letters for each respective protocol.

3. Product Quality

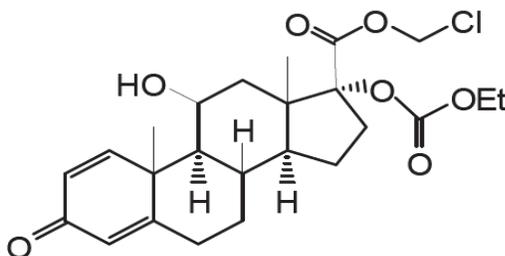
From the original Product Quality Review:

From the CMC perspective, this NDA is recommended for approval pending satisfactory resolution of all labeling and nomenclature issues.

Note: In the wrap-up meeting held September 14, 2012, CMC stated that while they recommend the use of “suspension” as the established name, they would not object to the use of “gel.”

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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



Molecular formula: C₂₄H₃₁ClO₇

Molecular weight: 466.96

DRUG PRODUCT NAME/CODE/TYPE:

- Proprietary Name: To be Determined
- Non-Proprietary Name (USAN): loteprednol etabonate ophthalmic gel, 0.5%
- Code Name/# (ONDC only):
- Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

DRUG SUBSTANCE:

Non-sterile drug substance specifications

Test	Analytical Procedure	Acceptance Criteria
Description	Visual, PS-1008	(b) (4)
Identification	IR, USP<197K>	
Residue on Ignition	USP<281>	
Loss on Drying ¹	USP<731>	
Particle Size	(b) (4) C-1572	
Related Substances ¹	C-1289	
HPLC Total Impurities ¹	C-1289	
Residual Solvents	C-1675	
Heavy Metals	USP<231>	
Specific Rotation	USP<781S>	
Assay ¹	HPLC, C-1289	
Bioburden ¹	USP<61>	

¹ Required for retest interval.
 VMD = Volume mean diameter

Sterile drug substance specifications

Test	Analytical Procedure	Acceptance Criteria	
Description ¹	Visual, PS-1008	(b) (4)	
Identification	IR, USP<197K>		
Residue on Ignition ²	USP<281>		
Loss on Drying ¹	USP<731>		
Particle Size ²	(b) (4) C-1572		
Related Substances ¹	C-1289		
Total HPLC Impurities ¹	C-1289		
Residual Solvents ²	C-1675		
Heavy Metals ²	USP<231>		
Specific Rotation ²	USP<781S>		
Assay ¹	HPLC, C-1289		
	(b) (4)		
Sterility ¹	USP<71>		Meets USP requirements Raw material is negative for growth after 14 days of incubation

¹ Required at retest interval.

² These tests may be transcribed from testing of the non-sterile drug substance as the results for these tests are not expected to change upon sterilization.

VMD = Volume mean diameter

DRUG PRODUCT:

The proposed dosage form for the drug product is Loteprednol Etabonate Ophthalmic Gel, 0.5%. It is described as a white to off white thixotropic gel for topical ophthalmic administration. The composition of the drug product is listed below.

Composition of Loteprednol Etabonate Ophthalmic Gel, 0.5%

Component	Reference to Quality Standard	Function	Concentration	
			mg/g	% w/w
Loteprednol etabonate (b)(4) sterile	In-house	Active	5.00	0.500
Edetate Disodium Dihydrate	USP/PhEur			
Glycerin, (b)(4)	USP/PhEur			
Propylene Glycol	USP/PhEur			
Boric Acid	NF/PhEur			
Polycarbophil	USP			
Sodium Chloride	USP/PhEur			
Tyloxapol	USP			
Sodium Hydroxide (b)(4)	In-house			
Benzalkonium Chloride Solution, (b)(4)	NF/PhEur	Antimicrobial Preservative		
Water for Injection	USP/PhEur			

† label claim for BAK is 30 ppm or 0.003%.
 (b)(4)

The proposed commercial drug product configurations include a nominal 5 g fill weight in a 10 mL LDPE bottle and a 0.5 g fill weight in a 4 mL LDPE bottle, both with (b)(4) tips, and pink polypropylene caps.

THIXOTROPIC PROPERTY:

Loteprednol Etabonate Ophthalmic Gel, 0.5% is an aqueous (b)(4) formulation containing (b)(4) (polycarbophil) (b)(4). B&L provided the plot of viscosity versus shear stress in the reproduced **Figure 3.2.P.2.2-1** (below). As shear stress decreases, viscosity increases exponentially. At shear stress of (b)(4) the viscosity is (b)(4).

Below a shear stress of (b)(4), viscosity is non-measurable (infinite). This is the “yield stress” below which the formulation meets the rheologic definition of a solid.

(b) (4)



REGULATORY SPECIFICATIONS:

From the NDA submission dated 7/27/12:

Table 3.2.P.5.1-1: Release and shelf life (stability) specifications for Loteprednol Etabonate Ophthalmic Gel

Test	Analytical Procedure (Type, #)	Acceptance Criteria	
		Release	Shelf Life
Description	Visual, PS-1008	White to off-white gel	White to off-white gel
Container Description	Visual, PS-1008	Not tested	A white plastic bottle with dropper tip and pink cap, with no significant discoloration or physical distortion.
Particulate Matter	Visual, PS-1013	Essentially free of foreign particulate matter	Not tested
Identification-HPLC	HPLC, 23-T211 or C-1849	The retention time for loteprednol etabonate peak in the sample corresponds to that of the standard	Not tested
Identification-UV	HPLC, 23-T211 or C-1849	The loteprednol etabonate peak in the sample and reference standard both exhibit a UV maximum at (b) (4)	Not tested
Loteprednol Etabonate Assay	HPLC, 23-T211 or C-1849	95.0 – 105.0% of label claim (LC = 0.5%)	90.0 – 110.0% of label claim (LC = 0.5%)
Content Uniformity Deliverable Containers NLT 5 g	USP<3> HPLC, 23-T211 or C-1849	Acceptance criteria A: 90 – 110% of label claim % RSD of n = 6 sample preparations = NMT (b) (4)	
Deliverable Containers LT 5 g		Acceptance criteria B: 90 – 110% of label claim % RSD of n = 12 sample preparations = NMT (b) (4)	
Related Substances:	HPLC, 23-T212 or C-1850	90 – 110% of label claim for n = 4 sample preparations	
(b) (4)		NMT (b) (4)	NMT (b) (4)
		NMT	NMT
Total related substances		NMT	NMT

Test	Analytical Procedure (Type, #)	Acceptance Criteria	
		Release	Shelf Life
Benzalkonium Chloride Assay	HPLC, 23-T222 or C-1851	90 – 110% of label claim (LC = 0.003%)	80 – 120% of label claim (LC = 0.003%)
Particle Size Distribution	C-1834 (b) (4)	(b) (4)	(b) (4)
pH	USP<791>	6.1 – 6.9	6.0 – 7.0
Viscosity	USP<911>	950 – 1800 cps	900 – 1900 cps
Osmolality	USP<785>	250 – 300 mOsm/kg	245 – 340 mOsm/kg
Sterility	USP<71> and PhEur 2.6.1	Meets USP and PhEur requirements	Meets USP and PhEur requirements
Antimicrobial Effectiveness [^]	USP<51>	Not tested	Meets USP requirements
Weight Loss/Gain	Manual, TP-8179 or C-1303	Not tested	NMT (b) (4)
Endotoxin	USP<85>	NMT (b) (4)	Not tested
Fill Weight	Weight Check (b) (4)	5 g: NLT (b) (4) 0.5 g: NLT (b) (4)	Not tested
(b) (4)	C-1878	Not tested	NMT (b) (4)

[^] This test will only be performed for the process validation batches and in the event of a BAK assay failure (below acceptance criterion) during stability testing.

* A fill weight of NLT (b) (4) or NLT (b) (4) will ensure that the weight of 5 g or 0.5 g respectively, is delivered from the container at the time of release.

NMT = not more than

NLT = not less than

LT = less than

INSPECTIONS:

An “Acceptable” site recommendation from the Office of Compliance has been made (March 20, 2012)

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 SUMMARY REPORT**

Application:	NDA 202872/000	Sponsor:	BAUSCH AND LOMB
Org. Code:	590		7 GIRALDA FARMS STE 1001
Priority:	3		MADISON, NJ 07940
Stamp Date:	29-NOV-2011	Brand Name:	LOTEPREDNOL ETABONATE OPHTHALMIC GEL, 0.
PDUFA Date:	29-SEP-2012	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	30-MAR-2012	Product Number; Dosage Form; Ingredient; Strengths	001; GEL; LOTEPREDNOL ETABONATE; .5%

FDA Contacts:	A. CUFF	Project Manager	(HF-01)	3017964061
	L. QI	Review Chemist		3017961438
	B. SHANMUGAM	Team Leader		3017961457

Overall Recommendation:	ACCEPTABLE	on 20-MAR-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 03-FEB-2012	by EES_PROD		
	ACCEPTABLE	on 02-FEB-2012	by D. SMITH	(HFD-323)	
	PENDING	on 22-DEC-2011	by EES_PROD		
	PENDING	on 22-DEC-2011	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
		(b) (4)	
DMF No:			AADA:
Responsibilities:		(b) (4)	
	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-MAR-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 1313525 FEI: 1313525
BAUSCH AND LOMB INC

DMF No: ROCHESTER, , UNITED STATES 14609 **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
(b) (4)
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-DEC-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: 1052807 FEI: 1000113778
BAUSCH AND LOMB PHARMACEUTICALS INC

DMF No: TAMPA, , UNITED STATES 336371014 **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
(b) (4)
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: STERILE OINTMENT **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JAN-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	CFN: (b) (4)	FEI: (b) (4)
DMF No:	(b) (4)	AADA:
Responsibilities:	(b) (4)	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	28-DEC-2011	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	
<hr/>		
Establishment:	CFN: (b) (4)	FEI: (b) (4)
DMF No:	(b) (4)	AADA:
Responsibilities:	(b) (4)	
Profile:	(b) (4)	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	28-DEC-2011	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	
<hr/>		
Establishment:	CFN: (b) (4)	FEI: (b) (4)
DMF No:	(b) (4)	AADA:
Responsibilities:	(b) (4)	
Profile:	(b) (4)	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	23-FEB-2012	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-DEC-2011
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-DEC-2011
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-FEB-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review:

From a pharmacology/toxicology perspective, approval is recommended.

The applicant referred to loteprednol etabonate previously approved NDAs (Lotemax®, Zylet®, and Alrex®) for most of the nonclinical information pertaining to the pharmacology and pharmacokinetics studies. The toxicology studies consists of ocular and systemic studies, complete genotoxicity battery, developmental and reproductive toxicity, and sensitization studies. The GLP-compliant toxicology package was submitted previously as part of NDA 20583, with additional studies submitted under NDA 50804 (Zylet®) and NDA 200738 (Lotemax Ointment®).

To specifically support the development and registration of the loteprednol etabonate (LE) gel formulation, three pharmacokinetic ocular distribution studies and two repeat dose ocular toxicology studies were conducted in rabbits. Table 1 outlines these studies. The *in vivo* pharmacokinetic distribution studies were conducted to characterize the ocular and systemic pharmacokinetic profile of loteprednol etabonate after topical ocular administration of the polycarbophil-based gel to rabbits. The pharmacokinetic studies were conducted with loteprednol etabonate formulations containing either 30ppm or 50ppm benzalkonium chloride (BAK), and up to 1% of loteprednol etabonate. The two toxicology studies evaluated the safety profile of the LE new gel. The toxicology studies included a 29-day repeat topical ocular dose study in rabbits and a 27-day systemic exposure to loteprednol etabonate. Both ocular toxicology studies were GLPcompliant.

The ocular toxicology studies were conducted with loteprednol etabonate gel formulations containing 50 ppm benzalkonium chloride (BAK) and up to 0.7% of loteprednol etabonate. See Sponsor’s Table 2 for a detailed description. All the studies mentioned above have been reviewed by Dr. Conrad Chen in Oct. 2009 under IND 102654. Based on the vast human experience with marketed loteprednol etabonate ophthalmic products and the previously conducted nonclinical ocular toxicity studies along with bridging ocular studies with new formulation, the proposed clinical studies under this IND were concluded to be safe to proceed.

Table 1: List of nonclinical studies conducted to support loteprednol etabonate, LE, gel formulation

Type of study	Test system	Route of administration	Study No.
Pharmacology	No new nonclinical studies were conducted to support the gel formulation		
Pharmacokinetics			
Distribution	Ocular PK – LE dose vs exposure with gel formulation in rabbits	Ocular	BL08009
	Ocular PK – Formulation comparison of gel formulation vs Lotemax in rabbits	Ocular	BL08010
Toxicology			
Repeat dose studies	29-day toxicology in rabbits using the gel formulation	Ocular	6104-275
	27-day toxicology/toxicokinetics in rabbits using the gel formulation	Ocular	6104-295

Summary of pharmacokinetics distribution studies: The polycarbophil based formulation afforded somewhat higher ocular exposure in tears and conjunctiva, but the exposure in cornea and aqueous humor was similar to the marketed products. According to the applicant, the systemic exposure to loteprednol etabonate following ocular administration of the polycarbophil-based formulation was very low, consistent with that observed with the Lotemax® formulation. The plasma loteprednol etabonate concentrations were < 1 ng/mL in most animals.

In a separate study examining the ocular and systemic pharmacokinetics using the gel formulation, loteprednol etabonate was rapidly absorbed and widely distributed to ocular tissues and plasma following a single topical ocular dose in rabbits with measurable concentrations detected in all ocular tissues at least 12 h after dosing. Systemic exposure to loteprednol etabonate was low, but measurable at 4 h after dosing. Large inter-animal variability was observed in all ocular tissues and plasma samples.

The results from the three ocular PK studies using the polycarbophil gel formulation indicate that ocular exposure to loteprednol etabonate following topical ocular administration in a polycarbophil gel formulation is similar or somewhat greater (1.2 to 3.0 fold) than that observed with the Lotemax suspension.

Summary of repeat dose toxicology studies: In a 29-day repeat dose ocular toxicity study in rabbits with 7-day recovery period, there were no significant ocular findings reported during the course of the study and the ocular toxicology study NOAEL was 0.7%. Decrease in actively growing hair follicles, evident in both the eyelids of treated animals, was observed; the eyelashes and meibomian glands were not affected. This was concluded to be related to a dermal exposure to the test article during dosing and is consistent with the known steroid modulation of their follicle cycling. Systemically, there were decreases in absolute and relative adrenal weights with a histopathologic correlate of cortical atrophy observed. The systemic NOAEL was less than 0.4%. The systemic effects of topical corticosteroids were typical of those observed in other studies.

In a 27-day repeat dose ocular toxicokinetic study in rabbits, the systemic exposure to loteprednol etabonate was demonstrated in all treated animals. After the 4th dose on Day 1, there was an increase in systemic exposure with an increase in dose concentration from 0.4% to 0.7%. The increase in C_{max} was less than dose proportional, but the AUC was approximately dose proportional. On Day 27, the increase in dose level did not result in an increase in C_{max} or AUC, and no accumulation of loteprednol etabonate was observed between Day 1 and Day 27.

Labeling: For all nonclinical sections of the label i.e. mechanism of action, pregnancy category, nursing mothers, women of childbearing potential, genetic and reproductive toxicology, the proposed labeling is proposed to be similar to that of loteprednol etabonate ophthalmic suspension 0.5% (Lotemax® - NDA (b)(4)) and loteprednol etabonate ophthalmic ointment, 0.5% (Lotemax®- NDA 200738).

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review:

There were no Clinical Pharmacokinetics studies conducted specifically for Lotemax (loteprednol etabonate, LE) ophthalmic gel 0.5%. The reviewer does not agree with the applicant's proposal to state in the LE gel package insert *12.3 Pharmacokinetics* that the

(b) (4)

(b) (4)

6. Sterility Assurance

From the original drug substance Product Quality Microbiology Review:

Recommend to approve from a quality microbiology standpoint.

The manufacturing process involves an

(b) (4)

(b) (4)

Analysis of Primary Endpoint(s)

The hierarchical primary efficacy endpoints for studies 576 and 577 were:

1. The proportion of subjects with complete resolution of anterior chamber cells at Visit 5 (Post-operative Day 8) for LE Gel and vehicle.
2. The proportion of subjects with Grade 0 (no) pain at Visit 5 (Post-operative Day 8) for LE Gel and vehicle.

Intent to Treat (ITT): The ITT population will include all randomized subjects.

Per Protocol (PP): The PP population will include all ITT subjects who remain in study through Visit 5 (Postoperative Day 8) and who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study.

Study 576 – ITT Population

Primary Efficacy Analysis	LE Gel N = 203	Vehicle N = 203	P-value
Complete Resolution of AC cells at Visit 5 (Post-operative Day 8)			
Yes	62 (30.5%)	33 (16.3%)	< 0.001
No	141 (69.5%)	170 (83.7%)	
Subjects without Rescue Medication	122	100	
Subjects with Rescue Medication	17	70	
Subjects with Missing Data	2	0	
Grade 0 (no) Pain at Visit 5 (Post-operative Day 8)			
Yes	148 (72.9%)	85 (41.9%)	< 0.001
No	55 (27.1%)	118 (58.1%)	
Subjects without Rescue Medication	36	48	
Subjects with Rescue Medication	17	70	
Subjects with Missing Data	2	0	

Study 576 – PP Population

Primary Efficacy Analysis	LE Gel N = 203	Vehicle N = 203	P-value
Complete Resolution of AC cells at Visit 5 (Post-operative Day 8)			
Yes	59 (30.4%)	28 (14.4%)	< 0.001
No	135 (69.6%)	166 (85.6%)	
Subjects without Rescue Medication	118	99	
Subjects with Rescue Medication	17	67	
Subjects with Missing Data	0	0	

Grade 0 (no) Pain at Visit 5 (Post-operative Day 8)			
Yes	143 (73.7%)	82 (42.3%)	< 0.001
No	51 (26.3%)	112 (57.7%)	
Subjects without Rescue Medication	34	45	
Subjects with Rescue Medication	17	67	
Subjects with Missing Data	0	0	

Study 577 – ITT Population

Primary Efficacy Analysis	LE Gel N = 206	Vehicle N = 201	P-value
Complete Resolution of AC cells at Visit 5 (Post-operative Day 8)			
Yes	64 (31.1%)	28 (13.9%)	< 0.001
No	142 (68.9%)	173 (86.1%)	
Subjects without Rescue Medication	134	124	
Subjects with Rescue Medication	6	47	
Subjects with Missing Data	2	2	
Grade 0 (no) Pain at Visit 5 (Post-operative Day 8)			
Yes	156 (75.7%)	92 (45.8%)	< 0.001
No	50 (24.3%)	109 (54.2%)	
Subjects without Rescue Medication	42	60	
Subjects with Rescue Medication	6	47	
Subjects with Missing Data	2	2	

Study 577 – PP Population

Primary Efficacy Analysis	LE Gel N = 187	Vehicle N = 186	P-value
Complete Resolution of AC cells at Visit 5 (Post-operative Day 8)			
Yes	61 (32.6%)	26 (14.0%)	< 0.001
No	126 (67.4%)	160 (86.0%)	
Subjects without Rescue Medication	121	114	
Subjects with Rescue Medication	5	46	
Subjects with Missing Data	0	0	
Grade 0 (no) Pain at Visit 5 (Post-operative Day 8)			
Yes	143 (76.5%)	84 (45.2%)	< 0.001
No	44 (23.5%)	102 (54.8%)	
Subjects without Rescue Medication	39	56	
Subjects with Rescue Medication	5	46	
Subjects with Missing Data	0	0	

The ITT and PP analyses are similar in both trials. There are statistically significant differences between LE gel and vehicle in the proportion of patients with complete resolution of AC cells at Day 8 and in Grade 0 (no) Pain at Day 8.

The hierarchical primary efficacy endpoints (complete resolution of AC cells and no pain at post-operative Day 8/ Visit 5) were compared between the LE Gel and vehicle treatment groups for the following subpopulations: age (< 65 years, $\geq 65 < 75$ years and ≥ 75 years), gender, and race (white and non-white).

The treatment effects were observed consistently across the subpopulations except for the most elderly age group. In the most elderly group (≥ 75 years), LE Gel was superior to vehicle in the treatment of pain (< 0.001) but not in the complete resolution of AC cells ($p=0.087$). The studies were not powered to demonstrate statistically significant differences for subgroups. A trend favoring loteprednol over vehicle exists for all subgroups.

Summary Efficacy Statement

Adequate and well controlled studies (Study 576 and Study 577) support the efficacy of loteprednol ophthalmic gel 0.5% for the treatment of post-operative inflammation and pain following ocular surgery.

There are statistically significant differences between LE gel and vehicle in the proportion of patients with complete resolution of AC cells at Day 8 and in Grade 0 (no) Pain at Day 8.

8. Safety

From the original Medical Officer Review:

The main support for efficacy is from the 2 clinical studies, Study 576 and Study 577.

Exposure

A total of 409 patients were exposed to LE Gel during development.

Study 576 - Treatment Exposure (Safety Population)

	LE Gel N=203	Vehicle N=203
Days of Exposure		
Mean (SD)	12.3 (3.46)	9.2 (4.87)
Median	14.0	8.0
Minimum	1	1
Maximum	16	16

Study 577 - Treatment Exposure (Safety Population)

	LE Gel N=206	Vehicle N=201
Days of Exposure		
Mean (SD)	13.2 (2.33)	10.2 (4.56)
Median	14	13
Minimum	2	1
Maximum	19	16

Deaths

No deaths were reported during the clinical development of LE Gel.

Dropouts and/or Discontinuations

Reason for Discontinuation	Study 576		Study 577	
	LE Gel N=203 n (%)	Vehicle N=203 n (%)	LE Gel N=206 n (%)	Vehicle N=201 n (%)
Withdrawal by subject	2 (1.0)	1 (0.5)	0	0
Lost to follow-up	0	0	0	0
Administrative issue	0	0	0	0
Adverse event	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Investigator decision	0	1 (0.5)	0	2 (1.0)
Failure to follow study procedures	0	0	0	1 (0.5)
Other	1 (0.5)	2 (1.0)	1 (0.5)	1 (0.5)

Adverse Events Associated with Discontinuation – Study 576

Patient	Age	Sex	Treatment	Days on Treatment	Adverse Event
2912	66	M	LE Gel	7	CME
2930	77	F	Vehicle	9	Pupillary membrane formation

Adverse Events Associated with Discontinuation – Study 577

Patient	Age	Sex	Treatment	Days on Treatment	Adverse Event
5314	70	F	LE Gel	6	Diverticulitis
6017	74	F	LE Gel	6	Cholecystitis
5202	73	M	Vehicle	8	Increased IOP

These adverse events are consistent with the age and general findings in the population of subjects undergoing cataract extraction.

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 576 - Ocular Treatment-Emergent AEs in $\geq 1\%$ of Study Eyes - Safety Population

	LE Gel N=203	Vehicle N=203	p-value
Total number of AEs	60	71	
Number of subjects with at least one AE	38 (18.7%)	44 (21.7%)	0.537
AC inflammation	8 (3.9%)	10 (4.9%)	0.810
Eye pain	5 (2.5%)	8 (3.9%)	0.575
Photophobia	4 (2.0%)	9 (4.4%)	0.259
Foreign body sensation	6 (3.0%)	4 (2.0%)	0.751
Conjunctival hemorrhage	5 (2.5%)	1 (0.5%)	0.215
Eye pruritus	2 (1.0%)	3 (1.5%)	>0.999
AC cells	1 (0.5%)	3 (1.5%)	0.623
Corneal edema	3 (1.5%)	1 (0.5%)	0.623
Vision blurred	1 (0.5%)	3 (1.5%)	0.623
Lacrimation increased	3 (1.5%)	0 (0.0%)	0.248
Posterior capsule opacification	3 (1.5%)	0 (0.0%)	0.248
IOP increased	3 (1.5%)	3 (1.5%)	>0.999

Study 576 – Non-ocular Treatment-Emergent AEs in $\geq 1\%$ of Study Eyes - Safety Population

	LE Gel N=203	Vehicle N=203	p-value
Total number of AEs	17	11	
Number of subjects with at least one AE	9(4.4%)	9 (4.4%)	>0.999
Nausea	3 (1.5%)	1 (0.5%)	0.623
Bronchitis	2 (1.0%)	2 (1.0%)	>0.999
Headache	1 (0.5%)	2 (1.0%)	>0.999

Study 577 - Ocular Treatment-Emergent AEs in $\geq 1\%$ of Study Eyes - Safety Population

	LE Gel N=206	Vehicle N=201	p-value
Total number of AEs	37	77	
Number of subjects with at least one AE	33 (16.0%)	58 (28.9 %)	0.002
AC inflammation	7 (3.4%)	14 (7.0%)	0.120

Eye pain	3 (1.5%)	10 (5.0%)	0.051
Iritis	4 (1.9%)	5 (2.5%)	0.748
Foreign body sensation	2 (1.0%)	4 (2.0%)	0.455
Dry eye	3 (1.5%)	2 (1.0%)	>0.999
Eye irritation	1 (0.5%)	3 (1.5%)	0.367
Ocular hyperemia	1 (0.5%)	3 (1.5%)	0.367
Photophobia	1 (0.5%)	3 (1.5%)	0.367
Lacrimation increased	3 (1.5%)	0 (0.0%)	0.248
Ocular discomfort	0 (0.0%)	3 (1.5%)	0.120
IOP increased	1 (0.5%)	7 (3.5%)	0.035

Study 577 – Non-ocular Treatment-Emergent AEs in ≥1% of Study Eyes - Safety Population

	LE Gel N=206	Vehicle N=201	p-value
Total number of AEs	17	15	
Number of subjects with at least one AE	12 (5.8%)	5 (2.5%)	>0.136
Headache	3 (1.5%)	1 (0.5%)	>0.999
Rash	2 (1.0%)	0 (0.0%)	0.499

Over all, the most common adverse drug reactions were anterior chamber inflammation (4%), eye pain (2%) and foreign body sensation (2%)

Nonfatal Serious Adverse Events

Patient	Timing of SAE	SAE	Narrative of SAE
Site #130068 Subject #1020	Prior to randomization	Syncope, electrolyte imbalance	79-year old male with a history of transient ischemic attack experienced two episodes of syncope and was diagnosed with an electrolyte imbalance. The subject was hospitalized and noted to be hyponatremic, hypokalemic, and hypomagnesemic. Two days after the onset of symptoms, the event resolved.
Site #726415 Subject #1617	Occurred after randomization	Bronchitis, exacerbated systolic congestive heart failure	79-year old male with a history of congestive heart failure and ejection fraction of 30% to 40%, began study medication (vehicle) on 22 Apr 2010 until 05 May 2010. On (b) (6) the subject was hospitalized for respiratory symptoms. A diagnosis of bronchitis and exacerbated systolic congestive heart failure was made. While hospitalized, the subject was treated. The subject was discharged on (b) (6) as the events resolved.
Site #979176 Subject #2115	Occurred after randomization	CME	76-year old female began the study medication (LE Gel) on 15 Mar 2010. On 16 Apr 2010 at Visit 6, the subject experienced blurred and distorted vision of the right eye; a diagnosis of CME was confirmed that day. The subject's pinhole Snellen VA OD on 2 Apr 2010 was 20/25. On 9 Apr 2010, her VA OD was 20/50 and on 16 Apr 2010 VA worsened to 20/60 in the right eye. On 19 Apr 2010, VA in the right eye improved to 20/40. The subject had no documented history of CME prior to the event. The

Patient	Timing of SAE	SAE	Narrative of SAE
			Investigator evaluated the event as moderate in intensity and is ongoing.
Site #979176 Subject #2119	Occurred after randomization	CME	82-year old female began the study medication (vehicle) on 24 Mar 2010 in the left eye. On 23 Apr 2010 at Visit 6, the subject experienced blurred and distorted vision secondary to CME in the left eye. The subject's VA on 09 Apr 2010 was 20/30. On 23 Apr 2010, her vision in the left eye was 20/40. The subject had no documented history of CME prior to the event. As of 15 Jun 2010, the Investigator considered the event resolved.

Study -577 – Nonfatal SAEs

Patient	Timing of SAE	SAE	Narrative of SAE
Site #150101 Subject #5314	Occurred after randomization	Acute diverticulitis episode	70-year old female with a history of episodic acute diverticulitis (b)(6) began study medication (LE Gel) on 04 May 2010 through 09 May 2010 (initial screening visit was 29 Apr 2010). On (b)(6) the subject experienced acute intestinal discomfort and pain She was diagnosed with an acute diverticulitis episode and was discharged from the hospital with the recommendation that a sigmoidoscopy be scheduled later that month (to allow time for the inflammation to subside). The SAE was considered resolved with sequelae (diverticulitis) on (b)(6). On (b)(6) she underwent a laparoscopic hand-assisted sigmoid colectomy with mobilization of splenic flexure, with coloproctoanastomosis. The subject tolerated the procedure well without complication.
Site #797349 Subject #6017	Occurred after randomization	Cholecystitis	74-year old female with a history of cholelithiasis began study medication (LE Gel) on 21 Jul 2010 until 05 Aug 2010. On (b)(6) the subject was hospitalized due to a sudden onset of abdominal pain. She was diagnosed with cholecystitis with secondary abdominal infection. The subject underwent gallbladder surgery with placement of three drainage bags; she developed a postoperative body rash after being given oral antibiotics (medication unknown). The subject was discharged from the hospital on (b)(6). On (b)(6) the SAE was considered recovered with sequelae.
Site #836315 Subject #1501	Occurred after randomization	Myocardial infarction	63-year old female with a history of hyperlipidemia, hypertension, diabetes and slight mitral valve regurgitation began study medication (LE Gel) on 08 Jun 2010 until 20 Jun 2010. On (b)(6) the subject was hospitalized with chest pain. The following procedures were performed: left heart catheterization, left ventriculogram, coronary angiography, right femoral angiography, percutaneous transluminal coronary angioplasty and stenting of the proximal right coronary artery. The subject's final diagnosis was myocardial infarction in the inferior wall. The event resolved with the sequelae of coronary disease with stent placement, as of (b)(6).
Site #863291 Subject #6334	Occurred after randomization	Hypokalemia, dehydration	60-year old female with a medical history significant for Type II insulin dependent diabetes mellitus, gastric bypass surgery, chronic pain, hypothyroidism, and severe anxiety with depression was administered study medication (vehicle) from 22 Jul 2010 through 03 Aug 2010. (b)(6) the

Patient	Timing of SAE	SAE	Narrative of SAE
			subject was seen in the emergency room three times, for events including hallucinations, anxiety, and a fall with a scalp laceration requiring sutures (considered nonserious adverse events). She was subsequently admitted to the hospital from (b) (6) (b) (6) with diagnoses of hypokalemia and dehydration. She had altered mentation. She was treated with intravenous fluids and was gradually advanced to tolerate a normal diet. She had a psychiatric evaluation, at which time it was recommended that she reinstitute appropriate psychiatric medications. The subject was reportedly to be transferred to a skilled nursing or assisted living facility to assist the subject with medications for further care.
Site #120032 Subject #3107	Occurred after study exit	Possible diagnosis of Creutzfeld-Jacob disease	76-year old male with a history of systemic hypertension, underwent cataract surgery on (b) (6) and began study medication (LE Gel) on 23 Jul 2010 through 04 Aug 2010 in the right eye. On 16 Aug 2010, the subject presented with symptoms of decreased visual acuity bilaterally (with scotoma), problems with orientation, and visual agnosia. Further information was provided on (b) (6) indicating the subject was hospitalized for additional neurological testing and work-up. He continued to have profound bilateral visual impairment and abnormal neurological symptoms. The subject's study article was unmasked by the Investigator (at the family's request), in order to evaluate all potential causes of visual impairment. Follow-up information was received on (b) (6) at which time, a possible diagnosis of Creutzfeld-Jacob disease was rendered. The subject reportedly died on (b) (6). The diagnosis of CJD could not be confirmed since the subject's family refused an autopsy.

These adverse events are consistent with the age and general findings in the population of subjects undergoing cataract extraction.

Drug- Specific Safety Explorations

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

Study 576: IOP Change From Baseline Prior to Rescue Medication Use Visit 7 (Safety Population)

	LE Gel N=203	Vehicle N=203
Visit 7 (POD# 18)		
Mean (SD)	-1.0 (3.64)	-1.9 (3.92)
≤ -5	21 (16.3%)	15 (25.0%)
-4 to 0	68 (52.7%)	30 (50.0%)
1 to 4	32 (24.8%)	12 (20.0%)
5 to 9	8 (6.2%)	3 (5.0%)
10-14	0	0

	LE Gel N=203	Vehicle N=203
≥ 15	0	0
Subjects with change in IOP ≥ 5 mm Hg	8 (6.2%)	3 (5.0%)
Subjects with CFB in IOP ≥ 10 mmHg	0	0
Subjects with treatment emergent IOP ≥ 30 mm Hg	0	0

Study 577: IOP Change From Baseline Prior to Rescue Medication Use Visit 7 (Safety Population)

	LE Gel N=206	Vehicle N=201
Visit 7 (POD# 18)		
Mean (SD)	-1.3 (3.73)	-1.1 (3.24)
≤ -5	26 (15.8%)	11 (12.9%)
-4 to 0	102 (61.8%)	47 (55.3%)
1 to 4	31 (18.8%)	24 (28.2%)
5 to 9	5 (3.0%)	3 (3.5%)
10-14	0	0
≥ 15	1 (0.6%)	0
Subjects with change in IOP ≥ 5 mm Hg	6 (3.6%)	3 (3.5%)
Subjects with CFB in IOP ≥ 10 mmHg	1 (0.6%)	0
Subjects with treatment emergent IOP ≥ 30 mm Hg	1 (0.6%)	0

Safety Summary Statement

The main support for efficacy is from the 2 clinical studies, Study 576 and Study 577.

Over all, the most common adverse drug reactions were anterior chamber inflammation (4%), eye pain (2%) and foreign body sensation (2%).

The nonfatal serious adverse events seen are consistent with the age and general findings in the population of subjects undergoing cataract extraction.

The four-month safety update was received on June 15, 2012. There was no new information to report.

9. Advisory Committee Meeting

An advisory committee meeting was not required for this application.

10. Pediatrics

The clinical trials did not enroll any pediatric patients. Safety and effectiveness in pediatric patients have not been established.

11. Other Relevant Regulatory Issues

BIOSTATISTICS

Per the original Biostatistics review:

Two primary efficacy endpoints were assessed at day 8 post-surgery: complete resolution (without rescue medication) of anterior chamber cell inflammation and complete resolution (without rescue medication) of pain. Anterior chamber cell inflammation is quantified by investigators in a 5-point grade scale (0 to 4) whereas ocular pain is assessed by patient and recorded by investigator in a 6-point grade scale (0 to 5). Complete resolution for each scale is defined as a grade of 0. In both endpoints, receiving rescue medication anytime before study visit is considered a treatment failure.

Based on the primary efficacy results as well as supportive analysis of secondary endpoints, we recommend approval of the product. The efficacy results on primary endpoint are summarized in the table below for proposed label. For proportion of anterior chamber cell resolution under treatment in randomized subjects, the effect size is 15% with 95% confidence interval of (6%, 23%) in study 576 and it is 17% with 95% confidence interval of (9%, 26%) in study 577. For proportion of ocular pain resolution under treatment in randomized subjects, the effect size is 31% with 95% confidence interval of (21%, 41%) in study 576 and 30% with 95% confidence interval of (20%, 39%) in study 577. Other exploratory analyses in the review support the efficacy claims by Applicant.

DPDP

The Division of Professional Drug Promotion (DPDP) was invited to team meetings for the loteprednol ophthalmic gel 0.5% application and participated in preliminary internal labeling discussions (midcycle 5/17/12 and wrap-up 9/14/12). They completed a formal review of the package insert.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) found the following

proprietary names unacceptable: (b) (4) in December 2011, (b) (4) in May 2012, (b) (4) in July 2012, and (b) (4) in September 2012.

As of September 14, 2012, the following proprietary names were still under consideration: (b) (4) Lotemax. The applicant, after discussion with DMEPA, has chosen to utilize Lotemax as the proprietary name for this product. In a letter dated 9/25/12, DMEPA found the proprietary name, Lotemax, acceptable.

In a review dated 3/8/2012, DMEPA had the following recommendations regarding the draft labeling with the proprietary name, (b) (4) submitted on 11/29/11. DMEPA has not reviewed subsequent labeling:

- 1) Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
- 2) The statement of strength lacks prominence. In order to increase the prominence of the strength, we recommend moving the statement of strength to appear underneath the established name and increasing the font size.
- 3) The manufacturer's name is overly prominent and competes for space with the proprietary name. Decrease the prominence of the manufacturer's name on the principal display panel (PDP) and relocate it away from the top third of the PDP.
- 4) The route of administration statement lacks prominence. Relocate the statement "For Ophthalmic Use Only" to the principal display panel immediately following the statement of strength.
- 5) Ensure the lot number and expiration date are printed on the label. The net quantity statement is too close to the strength. Relocate the net quantity away from the statement of strength and debold the font.
- 6) Remove the pink highlighting over the NDC number.

With the exception of item 1, Clinical does not agree with the proposed DMEPA revisions. The statement of strength is part of the name of the product and should not be placed on a separate line; the current proposed labeling is consistent with Loteprednol suspension and ointment products. The manufacturer's name is not overly prominent and is consistent with Loteprednol suspension and ointment products. The route of administration is essentially part of the established name of the product (ophthalmic gel), and the applicant is not required to place the route on the principle display panel. The net quantity is not too close to the strength; both are clearly legible. The pink highlighting does not obscure the NDC number.

FINANCIAL DISCLOSURE

Bausch and Lomb has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for loteprednol etabonate ophthalmic gel. One investigator who participated in the phase 3 Clinical Study 576 disclosed financial ties to the sponsor.

Investigators with financial Interests or Arrangements

Clinical Study	Investigators
576	Rajesh K. Rajpal, MD

This investigator only enrolled three patients in the study. Removal of the data from this site would have no significant impact on the final conclusions of either this study or the application as a whole.

OSI

An Office of Scientific Investigations (OSI) audit was requested.

Per the OSI review dated August 8, 2012:

Two domestic clinical investigators were selected for inspection. The sites were chosen on the basis of enrollment of large numbers of study subjects per site, large number of INDs in the OSI database, and absence of previous inspectional history.

Name of CI	Protocol # and # of Subjects:	Inspection Date	Final Classification
Douglas Lorenz, D.O. 870 Seven Hills Drive Suite # 202 Henderson. NV 89052 Site #580555	Study 576/ 35 subjects	April 4 to April 25, 2012	VAI
Robert J DaVanzo, M.D. Comerstone Eye Care 307 North Lindsay Street High Point, NC 27262 Site #140100	Study 577/ 40 subjects	March 27 to March 29, 2012	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

The final classification of Clinical Investigator inspection of Dr. Robert J DaVanzo is No Action Indicated (NAI). Based on the inspectional findings at this site, efficacy and safety data obtained from this site can be considered reliable in support of the application.

The final classification of Clinical Investigator inspection of Dr. Douglas Lorenz is Voluntary Action Indicated (VAI). Although regulatory violations were noted, these were not considered to have a significant impact on data reliability. Based on the inspectional findings at this site, efficacy and safety data obtained from this site can be considered reliable in support of the application.

A Form FDA 483, Inspectional Observations, was issued to this investigator [Dr. Douglas Lorenz], mainly for failure to conduct the study in accordance with the investigational plan and prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

12. Labeling

The labeling found in this Appendix (package insert and carton and container labeling submitted on 9/25/12) is acceptable.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 202872 for Lotemax (loteprednol ophthalmic gel) 0.5% is recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery.

The data contained in the clinical trials submitted in this submission (Studies 576 and 577) established the efficacy of loteprednol etabonate ophthalmic gel 0.5% in the treatment of post-operative inflammation and pain following ocular surgery. Studies 576 and 577 met their pre-specified hierarchical primary efficacy endpoints:

- 1) Complete resolution of anterior chamber cells at Post-operative Day 8, and
- 2) Grade 0 pain at Post-operative Day 8.

There are no new safety concerns raised in this NDA submission concerning the use of loteprednol etabonate ophthalmic gel 0.5% in the treatment of post-operative inflammation and pain following ocular surgery.

The benefit of loteprednol etabonate ophthalmic gel 0.5% in the treatment of post-operative inflammation and pain following ocular surgery has been demonstrated in this NDA application. The risk for using this drug is consistent with the currently marketed ophthalmic products with the same active pharmaceutical ingredient, loteprednol etabonate (Lotemax, Alrex, and Zylet).

9 pages of draft labeling has been withheld in full as
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
09/26/2012

WILEY A CHAMBERS
09/26/2012