CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202872Orig1s000

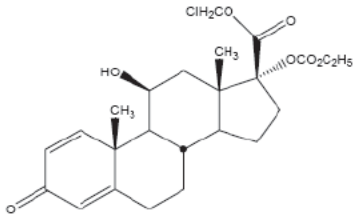
MEDICAL REVIEW(S)

Deputy Division Director Review for NDA 202-872

Date	September 27, 2012
From	Wiley A. Chambers, M.D.
NDA #	202-872
Applicant	Bausch & Lomb Incorporated
Date of Submission	November 29, 2011
Type of Application	505(b)(1)
Name	Lotemax (loteprednol etabonate ophthalmic gel) 0.5%
Dosage forms / Strength	Topical ophthalmic gel
Proposed Indication(s)	Treatment of post-operative inflammation and pain following ocular surgery
Recommended Action:	Approval

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 gel containing 0.5% loteprednol etabonate.



Loteprednol etabonate has been marketed in the United States 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 gel, 0.5% was conducted under IND 102,654.

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 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate. The molecular formula is $C_{24}H_{31}ClO_7$ 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% and Lotemax (loteprednolol etabonate ophthalmic ointment) 0.5%.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Component	Reference to Quality Standard	Function	Concentration (mg/g)	% w/w
Loteprednol Etabonate (b) (4) sterile	In-house	Active	5.0	0.500
Edetate Disodium Dihydrate	USP	(b) (4)		
Glycerin, (b) (4)	USP			
Propylene Glycol	USP			
Boric Acid	USP			
Polycarbophil	USP			
Sodium Chloride	USP			
Tyloxapol	USP			
Sodium Hydroxide (b) (4)	In-house	pH adjuster	To adjust pH to 6.4-6.7	Adjust pH to 6.4-6.7
Benzalkonium Chloride Solution, (b) (4)	NF	Antimicrobial Preservative	(b) (4)	(b) (4)
Water for Injection	USP	(b) (4)		

Label claim for BAK is 30 ppm or 0.003%

Commercial drug product will be packaged as a nominal 5g fill in 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.

Loteprednol Etabonate Ophthalmic Gel, 0.5% is an aqueous (b) (4) formulation containing a (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)

Drug Product Specifications:

Test	Analytical Procedure	Acceptance Criteria	
		Release	Shelf life
Description	Visual (PS-1008)	Off-white (b) (4)	
Particulate Matter	Visual (PS-1013)	Essentially free of foreign particulate matter	Not applicable
Particle Size Distribution	C-1834 (b) (4) (b) (4)	(b) (4)	Not applicable
Identification A	HPLC, 23-T211 or C-1849 (HPLC)	The retention time for loteprednol etabonate peak in the sample corresponds to that of the standard	Not applicable
Identification B	HPLC, 23-T211 or C-1849 (UV)	The UV spectrum of the assay preparation exhibits its maximum at the same wavelength as that of the standard	Not applicable
Loteprednol Assay	C-1849 (HPLC)	95.0 – 105.0% of label claim	90.0 – 110.0% of label claim
Content Uniformity Deliverable Container NLT 5g Deliverable Containers LT 5g	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) Acceptance criteria B: 90-110% of label claim % RSD of n=12 sample preparations = NMT (b) (4) 90-110% of label claim for n=4 sample preparations	
Related Substances	HPLC, 23-T212 or C-1850	(b) (4)	NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT NMT NMT	NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT NMT NMT
		Total related substances	NMT	NMT
		Total Chromatographic Related Substances	NMT	NM
Benzalkonium Chloride Assay	HPLC, 23-T222 or C-1851	90-110% of label claim	80-120% of label claim	
pH	USP,791>	6.1-6.9	6.0-7.0	
Viscosity	USP<911>	1050-1900 cps		1050-1900 cps
Fill Weight	Weight Check (b) (4)	5g: NLT (b) (4) 0.5 g: NLT (b) (4)		Not tested
Osmolality	USP<785?	250-300 mOsm/kg		245-340 mOsm/kg
Antimicrobial Effectiveness	USP<51>	Not tested		Meets USP requirements
Weight Loss/Gain	Manual, TP-8179 or C-1303	Not tested	NMT (b) (4)	
Sterility	USP <71> and PhEur 2.6.1	Meets USP and PhEur requirements		
(b) (4)	C-1878	Not tested	NMT (b) (4)	
Endotoxin	USP <85>	NMT (b) (4)		Not tested

3. Nonclinical Pharmacology/Toxicology

The nonclinical safety profile of loteprednol etabonate (LE) has been evaluated as a 0.5% ophthalmic suspension under NDA 20-583 (approved March 1998). 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. 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.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

There were no Clinical Pharmacokinetics studies conducted specifically for Lotemax (loteprednol etabonate ophthalmic gel) 0.5%.

5. Sterility Assurance

The manufacturing process involves an (b) (4)

(b) (4)

Specifications

- Endotoxin – NMT (b) (4)
- Sterility – Meets USP and PhEur requirements.
- Preservative - BAK assay with a specification of 90-110% of label claim.

- Antimicrobial Effectiveness (AET) – The antimicrobial testing method follows USP <51>. In routine production, this test will only be performed in the event of a BAK assay failure. The AET method suitability (verification) testing per USP <51> demonstrated the recovery of the challenge organisms in Dey Engley broth (DEB) and Letheen Broth (LEB). The verifications were performed on two lots; Lot 427611 in DEB media and Lot 537591 in LEB media. The acceptance criterion was at least a (b) (4) recovery of challenge microorganisms recovered for the test article compare to the inoculum controls. Recovery of *S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans*, and *A. brasiliensis* ranged from (b) (4) % with the DEB media and (b) (4) % in the LEB media.

6. Clinical/Statistical - Efficacy

Two clinical studies (Studies 576 and 577) were used to evaluate safety and efficacy of the gel formulation in addition to the previous studies conducted with loteprednol suspension and ointment.

Clinical/Statistical - Efficacy

Study 576: Inflammation Cleared Analysis (ITT Population)

	LE Gel N=203	**Vehicle N=203**	**P value**
Day 3	16 (8%)	10 (5%)	0.224
Day 8 – primary endpoint	60 (30%)	33 (16%)	0.001
Day 15	101 (50%)	44 (22%)	<0.001
Day 18	96 (47%)	45 (22%)	<0.001

Study 577: Inflammation Cleared Analysis (ITT Population)

	LE Gel N=206	**Vehicle N=201**	**P value**
Day 3	6 (3%)	6 (3%)	0.92
Day 8 – primary endpoint	63 (31%)	23 (11%)	<0.001
Day 15	115 (56%)	57 (28%)	<0.001
Day 18	113 (55%)	57 (28%)	<0.001

Study 576: Mean ACR Count (ITT Population)

	LE Gel (N=203)	**Vehicle (N=203)**
Visit 1-Screening	0	0
Visit 3-POD#1 (sd)	3.1 (0.9)	3.2 (0.8)
Visit 4-POD #3 (sd)	-1.0 (1.2)	-0.3 (1.3)
Visit 5-POD #8 (sd)	-1.7 (1.4)	-0.6 (1.6)
Visit 6-POD #15 (sd)	-2.0 (1.5)	-0.7 (1.7)
Visit 7-POD #18 (sd)	-2.0 (1.5)	-0.7 (1.7)

Study 577: Mean ACR Count (ITT Population)

	LE Gel	**Vehicle**
Visit 1-Screening	0	0
Visit 3-POD#1 (sd)	3.3 (0.8)	3.3 (0.9)
Visit 4-POD #3 (sd)	-1.2 (1.0)	-0.6 (1.4)
Visit 5-POD #8 (sd)	-2.0 (1.3)	-0.9 (1.6)
Visit 6-POD #15 (sd)	-2.6 (1.3)	-1.3 (0.8)
Visit 7-POD #18 (sd)	-2.6 (1.3)	-1.4 (0.9)

Study 576: Pain Free Analysis (ITT Population)

	LE Gel N=203	Vehicle N=203	P value
Day 3	153 (75%)	96 (47%)	<0.001
Day 8	148 (73%)	85 (42%)	<0.001
Day 15	154 (76%)	77 (38%)	<0.001
Day 18	121 (60%)	54 (27%)	<0.001

Study 577: Pain Free Analysis (ITT Population)

	LE Gel N=206	Vehicle N=201	P value
Day 3	139 (68%)	93 (46%)	<0.001
Day 8	156 (76%)	92 (46%)	<0.001
Day 15	160 (79%)	89 (44%)	<0.001
Day 18	172 (85%)	114 (57%)	<0.001

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic gel) 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.

Safety- 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.

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic gel) 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

7. Advisory Committee Meeting

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

8. Pediatrics

In June 2012, Bausch & Lomb submitted a revised study protocol to study pediatric patients, 0-ll years of age following ocular surgery. The results of this study are expected by December 2016. It is recommended that the pediatric plan be accepted and a deferral of pediatric information be considered because the application is otherwise ready for approval in adults.

9. Other Relevant Regulatory Issues

FINANCIAL DISCLOSURE
Bausch and Lomb has 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 had 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. 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.

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

The final classification of Clinical Investigator inspection of Dr. Douglas Lorenz was 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 was considered reliable in support of the application.

10. Labeling

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

8 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

11. Regulatory Action

Lotemax (loteprednol etabonate ophthalmic gel) 0.5% is recommended to be approved for the treatment of post-operative inflammation and pain following ocular surgery.

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

CMC, Pharmacology/Toxicology, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

It is recommended that Bausch & Lomb complete a post-marketing study to establish the safety of Lotemax (loteprednol etabonate ophthalmic gel) 0.5% in pediatric patients. It is expected that this post-marketing requirement could be fulfilled by completion of study #670: A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Cataract Surgery for Childhood Cataract. The results of this study should be submitted by December 31, 2016.

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products

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/s/

WILEY A CHAMBERS
09/27/2012

CLINICAL REVIEW

Application Type	N
Application Number(s)	NDA 202872
Priority or Standard	Standard
Submit Date(s)	May 20, 2010
Received Date(s)	November 29, 2012
PDUFA Goal Date	September 29, 2012
Division / Office	DTOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	September 21, 2012
Established Name	Loteprednol etabonate ophthalmic gel 0.5%
(Proposed) Trade Name	Lotemax
Therapeutic Class	Corticosteroid
Applicant	Bausch and Lomb
Formulation(s)	Ophthalmic gel
Dosing Regimen	One (1) to two (2) drops in the affected eye four times daily for 14 days
Indication(s)	Treatment of post-operative inflammation and pain following ocular surgery
Intended Population(s)	Patients ages 18 years and older with post-operative inflammation and pain

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 202-872 be approved with the labeling revisions found in this review.

1.2 Risk Benefit Assessment

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).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarket clinical study requirements and commitments.

2 Introduction and Regulatory Background

Loteprednol etabonate (LE) is a corticosteroid that was 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.

2.1 Product Information

Established Name:	loteprednol etabonate ophthalmic gel 0.5%
Proposed Trade Name:	Lotemax
Chemical Class:	new formulation
Pharmacological Class:	corticosteroid
Indication	treatment of post-operative inflammation and pain following ocular surgery
Dosing Regimen:	One or two drops into the conjunctival sac of the affected eye four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.
Age Groups:	adults 18 years of age and older

2.2 Tables of Currently Available Treatments for Proposed Indications

Name of Drug	Indication
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.
Lotemax Ointment	Treatment of post-operative inflammation and pain following ocular surgery
Lotemax Suspension	Treatment of post-operative 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, since 2005 in a fixed combination with tobramycin as Zylet, and since 2011 as Lotemax ophthalmic ointment.

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 conjunctivitides, 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.
Lotemax (loteprednol etabonate ophthalmic ointment, 0.5%)	200-738	Treatment of post-operative inflammation and pain following ocular surgery

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, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, and ptosis.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information requests for the sponsor.

There is no evidence that the studies reviewed in this supplemental BLA were not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

The clinical studies included in this application conform with Good Clinical Practices.

3.3 Financial Disclosures

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

Reviewer's Comments:

This investigator contributed only 3 patients to 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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Qualitative and Quantitative Composition of Loteprednol Etabonate Ophthalmic Gel

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	(b) (4)		
Glycerin, (b) (4)	USP/PhEur			
Propylene Glycol	USP/PhEur			
Boric Acid	NF/PhEur			
Polycarbophil	USP			
Sodium Chloride	USP/PhEur			
Tyloxapol	USP			
Sodium Hydroxide (b)	In-house	pH Adjuster	Adjust pH to 6.4 – 6.7	Adjust pH to 6.4 – 6.7
Benzalkonium Chloride Solution, (b) (4)	NF/PhEur	Antimicrobial Preservative	(b) (4)	
Water for Injection	USP/PhEur	(b) (4)		

[1] label claim for BAK is 30 ppm or 0.003%

(b) (4)

The formulation of loteprenol etabonate ophthalmic gel that was used in the clinical studies is the same as the formulation intended for marketing.

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 gel, the sponsor conducted a 29-day repeat topical ocular dose study in rabbits to establish the safety profile and a companion 27-day repeat topical ocular dose study in rabbits with toxicokinetic evaluation of systemic exposure to LE. The study reports showed no significant toxicity findings.

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.

See Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Loteprednol etabonate ophthalmic gel is topical, anti-inflammatory corticosteroid for ophthalmic use.

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 gel formulation.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol #	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
576 Safety/ efficacy study	Prospective, multi-center randomized, vehicle-controlled, double-masked	Patients 18 years of age and older undergoing cataract surgery	Loteprednol etabonate ophthalmic gel Vehicle	1-2 drops QID to study eye 1-2 drops	Approx. 14 days	406

				QID to study eye		
577 Safety/ efficacy study	Prospective, multi-center randomized, vehicle-controlled, double-masked	Patients 18 years of age and older undergoing cataract surgery	Loteprednol etabonate ophthalmic gel Vehicle	1-2 drops QID to study eye 1-2 drops QID to study eye	Approx. 14 days	407

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/Clinical Trials

Studies 576 and 577

The study title and design of studies 576 and 577 are identical.

Title: A Randomized, Multicenter, Double-Masked, Parallel-Group, Clinical Safety and Efficacy Evaluation of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Vehicle for the Treatment of Inflammation and Pain Following Cataract Surgery
Study Design

These studies were prospective, multi-center, double-masked, parallel group, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of LE ophthalmic gel, 0.5% compared to vehicle in the treatment of inflammation and pain following cataract surgery. Post-operatively, subjects were randomized in a 1:1 ratio to receive LE Gel or vehicle. Seven study visits were scheduled during the four-week study period.

Visit 1 was the Screening Visit. Visit 2 was the day of surgery. At Visit 3 (Post-operative Day 1), eligibility for randomization was assessed. Eligible subjects completed post-operative study Visits 4 through 7.

Subjects instilled one or two drops of masked study drug into the study eye four times a day, at approximately four hour intervals for 14 days. The initial dose occurred at Visit 3 (Post-operative Day 1). The last dose was administered on the day before Visit 6 (Postoperative Day 15). Visit 7 was a two week post-treatment follow-up performed at Post-operative Day 18).

Grading Scales Used for Studies 576 and 577

Cells: Use a high-power field slit beam of 1 mm x 1 mm. Assess accumulation of white blood cells in aqueous. Pigment cells and red blood cells are to be ignored.

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

Ocular Pain: A positive sensation of the eye, including foreign body sensation, stabbing, throbbing, or aching.

0 = None Absence of positive sensation.
1 = Minimal Presence of mild sensation or discomfort typical of postoperative ocular surgery (eg, 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 over the counter (OTC) analgesics (eg, acetaminophen).
4 = Moderately Severe More prolonged aching requiring the use of an OTC analgesic other than acetaminophen.
5 = Severe Intense ocular, periocular or radiating pain (eg, constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics.

APPENDIX A: SCHEDULE OF VISITS AND PARAMETERS

All study tasks should be performed by qualified study site personnel as indicated on the delegation of authority log under the supervision of the Principal Investigator. Furthermore, all ocular signs must be evaluated by an ophthalmologist.

PROCEDURE/ASSESSMENTS[1]	Visit 1 Screening	Visit 2 Surgery[2]	Visit 3 Postop Day 1[3]	Visit 4 Postop Day 3 (±1 Day)	Visit 5 Postop Day 8 (±1 Day)	Visit 6 Postop Day 15 (±1 Day)[4]	Visit 7 Postop Day 18 (±1 Day)
Informed Consent and HIPAA authorization	X						
Urine Pregnancy Test, as applicable	X						
Demographics	X						
Current and Relevant Medical/Ophthalmic History	X						
Ocular Symptoms	X		X	X	X	X	X
Study Drug Gel Comfort Assessment				X	X	X	
Pinholed 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)[5]	X		X	X	X	X	X
Determine Eligibility	X		X				
AEs[6] and Concomitant Medications	X	X	X	X	X	X	X
Weigh Study Drug			X	X	X	X	
Dispense Study Drug			X[7]				
Collect Study Drug						X	
Dispense and Collect Diary Cards			X[8]	X	X	X[9]	
Check Diary Cards for Accuracy and Compliance				X	X	X	
Exit Study							X

1) All ophthalmic assessments will be performed bilaterally. 2) Visit 2 must occur within 14 days of Visit 1. Screening and surgery cannot take place on the same day. 3) Visit 3 should occur 18 to 34 hours post-surgery. During this visit subject eligibility will be confirmed based on anterior chamber cells. 4) The assessments scheduled for Visit 6 should also be performed at an early termination visit. 5) IOP should be assessed within ±2 hours of the time IOP was assessed at the Screening Visit. 6) Collection of AEs extends from the time the subject gives informed consent until the last study visit. 7) Subjects should instill initial dose while in clinic. 8) Dispense only. 9) Collect only.

Inclusion Criteria

This study will include subjects who meet the following criteria at the Screening Visit:

1. Subjects who are at least 18 years of age on the date the Informed Consent Form (ICF) is signed and with the capacity to provide voluntary informed consent.
2. Subjects who have the ability to read, understand, and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF, and provide Health Insurance Portability and Accountability Act (HIPAA) authorization.
3. Subjects who are candidates for routine, uncomplicated cataract surgery (phacoemulsification with posterior chamber intraocular lens [IOL] implantation, not combined with any other surgery).
4. Subjects who, in the Investigator's opinion, have potential post-operative pinholed Snellen visual acuity (VA) of at least 20/200 in the study eye.
5. Subjects who are not of childbearing potential or female subjects who have a negative urine pregnancy test result at screening.
6. Subjects who are able and willing to comply with all treatment and follow-up/study procedures.

In addition, this study will include subjects who meet the following criteria at Visit 3 (Post-operative Day 1)

7. Subjects who have undergone routine, uncomplicated cataract surgery (phacoemulsification with posterior chamber IOL implantation, not combined with any other surgery).
8. Subjects who have ≥ Grade 2 anterior chamber cells.

Exclusion Criteria

This study will exclude subjects who meet the following criteria:

1. Subjects who are expected to require concurrent ocular therapy (either eye) with non-steroidal anti-inflammatory drugs (NSAIDs), mass cell stabilizers, anti-histamines, or decongestants during the 18 days following cataract surgery or have used any of the above within 2 days prior to surgery.
2. Subjects who are expected to require treatment with systemic NSAIDs during the 18 days following cataract surgery with the exception of ≤ 81 mg/day of acetylsalicylic acid.
3. Subjects who are expected to require treatment with systemic or ocular (either eye) corticosteroids (other than study drug) during the 18 days following cataract surgery or have used any systemic or ocular corticosteroids within 14 days prior to cataract surgery.
4. Subjects who are expected to require concurrent ocular therapy with immunosuppressants (e.g., Restasis) during the 18 days following cataract surgery or have used immunosuppressants within 30 days prior to surgery.

5. Subjects who have known hypersensitivity or contraindication to the study drug(s) or their components.
6. Subjects who have a history or presence of chronic generalized systemic disease that the Investigator feels might increase the risk to the subject or confound the result(s) of the study.
7. Subjects who have a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment or follow-up.
8. Subjects with elevated IOP (≥ 21 mmHg), uncontrolled glaucoma, or subjects being treated for glaucoma in the study eye.
9. Subjects who are monocular or have pinholed Snellen VA 20/200 or worse in the non-study eye.
10. Subjects who have 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.
11. Subjects who are sexually active and who do not fall into one of the following categories:
    - Postmenopausal
    - Surgically sterile
    - Using on e of the following birth control methods throughout the duration of the study:
        - intrauterine device (> 14 days of Screening Visit)
        - barrier method (condom or diaphragm) with spermicide (> 14 days of Screening Visit)
        - hormonal contraception (same dose and same formulation for at least 6 months of Screening Visit)
12. Women who are breastfeeding.
13. Subjects participating in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation.
14. Subjects who were previously randomized in this study.

NOTE: Limbal Relaxing Incisions (LRIs) are allowed, as long as in the post-surgical assessment, the Investigator does not feel that randomization into the study will pose additional risks to the subject. If an LRI is performed, it must be entered on the Ocular Surgical Intervention Log in the electronic Case Report Forms (eCRFs).

Subjects anticipated to require additional manipulations, for example those subjects taking Flomax, should not be screened. However, if these subjects are expected to undergo routine, uncomplicated cataract surgery (phacoemulsification with posterior chamber IOL implantation, not combined with any other surgery), they may be screened,

Primary Efficacy Variable(s)

The hierarchical primary efficacy endpoints for this study are:

1. The proportion of study eyes with complete resolution of anterior chamber cells at Visit 5 (Post-operative Day 8) for LE Gel and vehicle.

2. The proportion of study eyes with Grade 0 pain at Visit 5 (Post-operative Day 8) for LE Gel and vehicle.

Secondary Efficacy Variables

- Proportion of study eyes with complete resolution of anterior chamber cells at each visit and for each study eye's final on treatment visit
- Proportion of study eyes with Grade 0 pain at each visit and for each study eye's final on treatment visit.
- Proportion of study eyes with complete resolution of anterior chamber flare at each visit and for each study eye's final on treatment visit
- Proportion of study eyes with complete resolution of anterior chamber cells and flare at each visit and for each study eye's final on treatment visit
- Change from baseline to each follow-up visit in anterior chamber cells and anterior chamber flare combined and separately

Study 576 – Table of Investigators

Investigator	**Investigator #**	**# of Patients Enrolled**
Cable, Melissa, M.D. Independence, MO 64055	130068	31 (7.6%)
DeBarge, Lawrence M.D. Fort Oglethorpe, GA 30742	946209	20 (4.9%)
Depenbusch, Michael, M.D. Phoenix, AZ 85050	140069	21 (5.2%)
Flynn, William J., M.D. San Antonio, TX 78229	947208	20 (4.9%)
Ghafouri, Mohammad Cameron, M.D. Washington, DC 20017	170070	0 (0.0%)
Hartman, Paul, M.D. Rochester, NY 14618	461665	12 (3.0%)
Jorizzo, Paul, M.D. Medford, OR 97504	726415	18 (4.4%)
Katzman, Barry, M.D. San Diego, CA 92115	504607	26 (6.4%)
Long, Daniel A., M.D. Gretna, LA 70056	579556	24 (5.9%)
Lorenz, Douglas, D.O. Henderson, NV 89052	580555	35 (8.6%)
Malhotra, Ranjan, M.D. St. Louis, MO 63131	665474	21 (5.2%)
Modi, Satish, M.D. Poughkeepsie, NY 12603	979176	22 (5.4%)
Mondzelewski, James P., M.D.	708432	0 (0.0%)

Pittsburgh, PA 15243		
Panzo, Gregory J., M.D. Mt. Dora, FL 32757	260071	17 (4.2%)
Protzko, Eugene E., M.D. Bel Air, MD 21014	752391	34 (8.4%)
Rajpal, Rajesh K., M.D. McLean, VA 22102	813333	3 (0.7%)
Roel, Lawrence, M.D. Spartanburg, SC 29306	280072	38 (9.4%)
Rotberg, Michael H., M.D. Charlotte, NC 21014	508604	26 (6.4%)
Rubin, Benjamin, M.D. Pikesville, MD 21208	509603	0 (0.0%)
Tyson II, Farrell C., M.D. Cape Coral, FL 33904	976179	38 (9.4%)

Study 577 – Table of Investigators

Investigator	**Investigator #**	**# of Patients Enrolled**
Angella, Guy J., M.D. Pembroke Pines, FL 33028	110099	24 (5.9%)
Bartz-Schmidt, Karl-Ulrich, Prof. Dr. Med 72076 Tubingen, Germany	120032	13 (3.2%)
DaVanzo, Robert J., M.D. High Point, NC 27262	140100	40 (9.8%)
Dua, Harminder, Prof. Dr. Nottingham NG7 2UH, England, UK	140118	0 (0.0%)
El-Harazi, Sherif M., M.D., M.P.H. Glendale, CA 91205	150036	10 (2.5%)
Endl, Michael J., M.D. Amherst, NY 14228	150101	29 (7.1%)
Fong, Raymond, M.D. New York, NY 10013	160102	36 (8.8%)
Jong, Kevin Y., M.D. Houston, TX 77025	200104	28 (6.9%)
Leonardo, Donna, M.D. Lancaster, PA 17601	220105	19 (4.7%)
Mester, Ulrich, Prof. Dr. 66280 Sulzbach, Germany	230006	3 (0.7%)
Meyers, Toni Takiko, M.D. Sanata Barbara, CA 93101	230106	1 (0.2%)
Peace, James H., M.D. Inglewood, CA 90301	859295	24 (5.9%)
Pendleton, Robert, M.D., Ph.D. Oceanside, CA 92056	797349	15 (3.7%)

Shettle, Philip Lee, D.O. Largo, FL 33770	290107	14 (3.4%)
Shulman David G., M.D. San Antonio, TX 78209	712429	14 (3.4%)
Silverstein, Bruce E., M.D. Reading, CA 96002	863291	35 (8.6%)
Silverstein Steven M., M.D. Kansas City, MO 64133	490621	29 (7.1%)
Smith, Stephen E., M.D. Ft. Meyers, FL 33901	836315	6 (1.5%)
Sutton, James D., M.D. Ocean Springs, MS 39564	742400	5 (1.2%)
Taustine, Lloyd R., M.D. Louisville, KY 40217	992163	21 (5.2%)
Treft, Robert L., M.D. Layton, UT 84041	554576	2 (0.5%)
Weston, Jon-Marc, M.D. Roseburg, OR 97471	717424	13 (3.2%)
Wolstan, Barry J. M.D. Torrance, CA 90505	511601	26 (6.4%)

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is treatment of post-operative inflammation and pain following ocular surgery.

6.1.1 Methods

Description of the clinical trial design is contained in Section 5.3.

6.1.2 Demographics

Study 576 - Patient Demographics (ITT Population)

		Study	
		576	
Treatment Group		LE Gel	Vehicle
Total enrollment in study		203	203
	White	176 (86.7%)	182 (89.7%)

Race	Black/African American	20 (9.9%)	16 (7.9%)
	Asian	2 (1.0%)	3 (1.5%)
	Native Hawaiian/ Pacific Islander	1 (0.5%)	0 (0.0%)
	American Indian/ Alaskan Native	0 (0.0%)	1 (0.5%)
	Other Race	4 (2.0%)	1 (0.5%)
Age	Mean ± SD	69.3 (8.7%)	69.0 (9.8%)
	Median	69.0	71.0
	Minimum, Maximum	50, 91	36, 88
Gender	Male	94 (46.3%)	81 (39.9%)
	Female	109 (53.7%)	122 (60.1%)
Ethnicity	Not Hispanic and Not Latino	188 (92.6%)	189 (93.1%)
	Hispanic or Latino	15 (7.4%)	14 (6.9%)

Study 577 - Patient Demographics (ITT Population)

		Study	
		577	
Treatment Group		LE Gel	Vehicle
Total enrollment in study		206	201
Race	White	151 (73.3%)	149 (74.1%)
	Black/African American	22 (10.7%)	21 (10.4%)
	Asian	28 (13.6%)	25 (12.4%)
	Native Hawaiian/ Pacific Islander	0 (0.0%)	0 (0.0%)
	American Indian/ Alaskan Native	2 (1.0%)	2 (1.0%)
	Other Race	3 (1.5%)	4 (2.0%)
Age	Mean ± SD	68.3 (9.7%)	69.4 (9.6%)
	Median	69.0	71.0
	Minimum, Maximum	30, 89	43, 88
Gender	Male	82 (39.8%)	92 (45.8%)
	Female	124 (60.2%)	109 (54.2%)
Ethnicity	Not Hispanic and Not Latino	188 (92.6%)	189 (93.1%)
	Hispanic or Latino	15 (7.4%)	14 (6.9%)
Country	US	198 (96.1%)	193 (96.0%)
	Germany	8 (3.9%)	8 (4.0%)

6.1.3 Subject Disposition

Study 576 - Subject Disposition and Primary Reason for Discontinuation

Disposition and Discontinuation	LE Gel N (%)	Vehicle N (%)
Total Randomized	203	203
Treated	203 (100.0%)	203 (100.0%)
As randomized	200 (98.5%)	200 (98.5%)
Not as randomized	3 (1.5%)	3 (1.5%)
Safety Population	203 (100.0%)	203 (100.0%)
Completed	199 (98.0%)	198 (97.5%)
Discontinued	4 (2.9%)	5 (2.5%)
ITT Population	203 (100.0%)	203 (100.0%)
Completed	199 (98.0%)	198 (97.5%)
Discontinued	4 (2.9%)	5 (2.5%)
Per Protocol (PP) Population	194 (95.6%)	194 (95.6%)
Completed	191 (98.5%)	191 (98.5%)
Discontinued	3 (1.5%)	3 (1.5%)
Primary reason for Discontinuation		
Withdrawal by subject	2 (1.0%)	1 (0.5%)
Adverse event	1 (0.5%)	1 (0.5%)
Investigator decision	0 (0.0%)	1 (0.5%)
Other	1 (0.5%)	2 (1.0%)

Study 577 - Subject Disposition and Primary Reason for Discontinuation

Disposition and Discontinuation	LE Gel N (%)	Vehicle N (%)
Total Randomized	206	201
Treated	206 (100.0%)	201 (100.0%)
As randomized	201 (97.6%)	1960 (97.5%)
Not as randomized	5 (2.4%)	5 (2.5%)
Safety Population	206 (100.0%)	201 (100.0%)
Completed	204 (99.0%)	196 (97.5%)
Discontinued	2 (1.0%)	5 (2.5%)
ITT Population	206 (100.0%)	201 (100.0%)
Completed	204 (99.0%)	196 (97.5%)
Discontinued	2 (1.0%)	5 (2.5%)
Per Protocol (PP) Population	187 (90.8%)	186 (92.5%)
Completed	187 (100.0%)	183 (98.4%)
Discontinued	0 (0.0%)	3 (1.6%)
Primary reason for Discontinuation		
Adverse event	1 (0.5%)	1 (0.5%)
Investigator decision	0 (0.0%)	2 (1.0%)

Failure to follow study procedures	0 (0.0%)	1 (0.5%)
Other	1 (0.5%)	1 (0.5%)

6.1.4 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.

Primary Efficacy Analysis

The primary analyses of the primary efficacy endpoints will first test the difference in the proportion of study eyes with complete resolution of anterior chamber cells between treatments at Visit 5 (Postoperative Day 8) using the asymptotic Pearson chi-squared statistic. Further, a 95% confidence interval will be constructed around the difference in proportions of complete resolution at the Visit 5 (Postoperative Day 8) visit using asymptotic normal approximations. Secondarily, this endpoint will be tested using the asymptotic Cochran Mantel-Haenszel statistic adjusting for site.

If this test is statistically significant at the two-sided alpha = 0.05 level in favor of LE Ophthalmic Gel, 0.5%, then the difference in the proportion of study eyes with Grade 0 pain between treatments at the Visit 5 (Postoperative Day 8) visit will be tested using the asymptotic Pearson chi-squared statistic at the alpha = 0.05 level. A 95% confidence interval will be constructed around the difference in proportions of complete resolution at Visit 5 (Postoperative Day 8) using asymptotic normal approximations. Secondarily, this endpoint will be tested using the asymptotic Cochran Mantel-Haenszel statistic adjusting for site.

Analysis Population

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	

Reviewer's Comments:

The ITT and PP analyses are similar in both trials. There are statisticcally 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.

6.1.5 Analysis of Secondary Endpoints(s)

The planned secondary endpoints for this study included the following:

- Proportion of study eyes with complete resolution of anterior chamber cells at each visit and for each study eye's final on treatment visit
- Proportion of study eyes with Grade 0 pain at each visit and for each study eye's final on treatment visit.
- Proportion of study eyes with complete resolution of anterior chamber flare at each visit and for each study eye's final on treatment visit
- Proportion of study eyes with complete resolution of anterior chamber cells and flare at each visit and for each study eye's final on treatment visit
- Change from baseline to each follow-up visit in anterior chamber cells and anterior chamber flare combined and separately

Study 576 – ITT Population

Secondary Efficacy at Visit 4 (Post-operative Day 3)

Secondary Efficacy Analysis – Visit 4	LE Gel N = 203	Vehicle N = 203	P-value
Complete Resolution of AC cells			
Yes	17 (8.4%)	11 (5.4%)	0.240
No	186 (91.6%)	192 (94.6%)	
Subjects without Rescue Medication	184	190	
Subjects with Rescue Medication	0	2	
Subjects with Missing Data	2	0	
Complete Resolution of AC flare			
Yes	93 (45.8%)	66 (32.5%)	0.006
No	110 (54.2%)	137 (67.5%)	
Subjects without Rescue Medication	108	135	
Subjects with Rescue Medication	0	2	
Subjects with Missing Data	2	0	
Complete Resolution of AC cells and flare			
Yes	16 (7.9%)	10 (4.9%)	0.224
No	187 (92.1%)	193 (95.1%)	
Subjects without Rescue Medication	185	191	
Subjects with Rescue Medication	0	2	
Subjects with Missing Data	2	0	
Grade 0 (no) Pain			
Yes	153 (75.4%)	96 (47.3%)	< 0.001
No	50 (24.6%)	107 (52.7%)	
Subjects without Rescue Medication	49	105	
Subjects with Rescue Medication	0	2	
Subjects with Missing Data	1	0	

Reviewer's Comments:

There is not a significant difference between groups at Day 3 for complete resolution of AC cells. There is a significant difference between groups at Day 3 for Grade 0 (no) Pain.

Secondary Efficacy at Visit 5 (Post-operative Day 8)

Secondary Efficacy Analysis – Visit 5	LE Gel N = 203	Vehicle N = 203	P-value
Complete Resolution of AC cells			
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	
Complete Resolution of AC flare			
Yes	138 (68.0%)	76 (37.4%)	< 0.001
No	65 (32.0%)	127 (62.6%)	
Subjects without Rescue Medication	46	57	
Subjects with Rescue Medication	17	70	
Subjects with Missing Data	2	0	
Complete Resolution of AC cells and flare			
Yes	60 (29.6%)	33 (16.3%)	0.001
No	143 (70.4%)	170 (83.7%)	
Subjects without Rescue Medication	124	100	
Subjects with Rescue Medication	17	70	
Subjects with Missing Data	2	0	
Grade 0 (no) Pain			
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	

Secondary Efficacy at Visit 6 (Post-operative Day 15)

Secondary Efficacy Analysis – Visit 6	LE Gel N = 203	Vehicle N = 203	P-value
Complete Resolution of AC cells			
Yes	102 (50.2%)	44 (21.7%)	< 0.001
No	101 (49.8%)	159 (78.3%)	
Subjects without Rescue Medication	63	52	
Subjects with Rescue Medication	35	105	
Subjects with Missing Data	3	2	
Complete Resolution of AC flare			
Yes	151 (74.4%)	76 (37.4%)	< 0.001
No	52 (25.6%)	127 (62.6%)	
Subjects without Rescue Medication	14	20	
Subjects with Rescue Medication	35	105	
Subjects with Missing Data	3	2	
Complete Resolution of AC cells and flare			
Yes	101 (49.8%)	44 (21.7%)	< 0.001
No	102 (50.2%)	159 (78.3%)	
Subjects without Rescue Medication	64	52	
Subjects with Rescue Medication	35	105	
Subjects with Missing Data	3	2	
Grade 0 (no) Pain			
Yes	154 (75.9%)	77 (37.9%)	< 0.001
No	49 (24.1%)	126 (62.1%)	

Subjects without Rescue Medication	11	19	
Subjects with Rescue Medication	35	105	
Subjects with Missing Data	3	2	

Secondary Efficacy at Visit 7 (Post-operative Day 18)

Secondary Efficacy Analysis – Visit 7	LE Gel N = 203	Vehicle N = 203	P-value
Complete Resolution of AC cells			
Yes	96 (47.3%)	45 (22.2%)	< 0.001
No	107 (52.7%)	158 (77.8%)	
Subjects without Rescue Medication	33	15	
Subjects with Rescue Medication	72	140	
Subjects with Missing Data	2	3	
Complete Resolution of AC flare			
Yes	119 (58.6%)	58 (28.6%)	< 0.001
No	84 (41.4%)	145 (71.4%)	
Subjects without Rescue Medication	10	2	
Subjects with Rescue Medication	72	140	
Subjects with Missing Data	2	3	
Complete Resolution of AC cells and flare			
Yes	96 (47.3%)	45 (22.2%)	< 0.001
No	107 (52.7%)	158 (77.8%)	
Subjects without Rescue Medication	33	15	
Subjects with Rescue Medication	72	140	
Subjects with Missing Data	2	3	
Grade 0 (no) Pain			
Yes	121 (59.6%)	54 (26.6%)	< 0.001
No	82 (40.4%)	149 (73.4%)	
Subjects without Rescue Medication	8	6	
Subjects with Rescue Medication	72	140	
Subjects with Missing Data	3	3	

Study 576 - AC Cell and Flare Scores Change from baseline (CFB) at Each Visit

Secondary Efficacy Analysis	**LE Gel Mean CFB Score (SD)**	**Vehicle Mean CFB Score (SD)**	**P-value**
AC Cell Scores			
Visit 1 – Screening	0	0	
Visit 3 – Post-operative Day 1 (Baseline)	2.3 (0.47)	2.3 (0.46)	
Visit 4 – Post-operative Day 3	-0.7 (0.82)	-0.3 (0.92)	< 0.001
Visit 5 – Post-operative Day 8	-1.2 (0.95)	-0.5 (1.12)	< 0.001
Visit 6 – Post-operative Day 15	-1.5 (1.04)	-0.6 (1.14)	< 0.001
Visit 7 – Post-operative Day 18	-1.4 (1.05)	-0.6 (1.15)	< 0.001
AC Flare Scores			

Visit 1 – Screening	0	0	
Visit 3 – Post-operative Day 1 (Baseline)	0.9 (0.70)	0.9 (0.64)	
Visit 4 – Post-operative Day 3	-0.3 (0.66)	-0.0 (0.66)	< 0.001
Visit 5 – Post-operative Day 8	-0.5 (.77)	-0.1 (0.76)	< 0.001
Visit 6 – Post-operative Day 15	-0.6 (0.78)	-0.1 (0.77)	< 0.001
Visit 7 – Post-operative Day 18	-0.6 (0.78)	-0.1 (0.78)	< 0.001
Combined AC Cell and Flare Scores			
Visit 1 – Screening	0	0	
Visit 3 – Post-operative Day 1 (Baseline)	3.1 (0.89)	3.2 (0.83)	
Visit 4 – Post-operative Day 3	-1.0 (1.17)	-0.3 (1.33)	< 0.001
Visit 5 – Post-operative Day 8	-1.7 (1.40)	-0.6 (1.63)	< 0.001
Visit 6 – Post-operative Day 15	-2.0 (1.50)	-0.7 (1.65)	< 0.001
Visit 7 – Post-operative Day 18	-2.0 (1.51)	-0.7 (1.67)	< 0.001

Study 577 – Mean AC Cell and Flare Scores Change from baseline (CFB) at Each Visit

Secondary Efficacy Analysis	**LE Gel Mean CFB Score (SD)**	**Vehicle Mean CFB Score (SD)**	**P-value**
AC Cell Scores			
Visit 1 – Screening	0	0	
Visit 3 – Post-operative Day 1 (Baseline)	2.3 (0.49)	2.3 (0.46)	
Visit 4 – Post-operative Day 3	-0.8 (0.62)	-0.4 (0.82)	< 0.001
Visit 5 – Post-operative Day 8	-1.4 (0.82)	-0.6 (0.97)	< 0.001
Visit 6 – Post-operative Day 15	-1.8 (0.81)	-0.9 (1.13)	< 0.001
Visit 7 – Post-operative Day 18	-1.8 (0.84)	-1.0 (1.17)	< 0.001
AC Flare Scores			
Visit 1 – Screening	0	0	
Visit 3 – Post-operative Day 1 (Baseline)	1.0 (0.69)	1.1 (0.69)	
Visit 4 – Post-operative Day 3	-0.4 (0.59)	-0.2 (0.76)	< 0.001
Visit 5 – Post-operative Day 8	-0.7 (.72)	-0.2 (0.84)	< 0.001
Visit 6 – Post-operative Day 15	-0.8 (0.73)	-0.4 (0.90)	< 0.001
Visit 7 – Post-operative Day 18	-0.8 (0.71)	-0.4 (0.88)	< 0.001
Combined AC Cell and Flare Scores			
Visit 1 – Screening	0	0	
Visit 3 – Post-operative Day 1 (Baseline)	3.3 (0.84)	3.3 (0.89)	
Visit 4 – Post-operative Day 3	-1.2 (0.97)	-0.6 (1.38)	< 0.001
Visit 5 – Post-operative Day 8	-2.0 (1.31)	-0.9 (1.56)	< 0.001
Visit 6 – Post-operative Day 15	-2.6 (1.34)	-1.3 (1.83)	< 0.001
Visit 7 – Post-operative Day 18	-2.6 (1.34)	-1.4 (1.86)	< 0.001

Reviewer's Comments:

Beginning at Day 3 there are significant differences between AC cell scores and AC flare scores between groups.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

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, ≥ 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).

Reviewer's Comments:

The studies were not powered to demonstrate statistically significant differences for subgroups. A trend favoring loteprednol over vehicle exists in all groups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dosing regimen was studied (QID for 14 days) in both Studies 576 and 577.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term effectiveness was not evaluated. The duration of treatment for the subjects in these trials was no longer than 14 days. LE Gel is intended for short-term use for the treatment of inflammation and pain following ocular surgery. There is no indication of a relapse in the treated condition when therapy is discontinued at Day 14.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol #	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
576 Safety/ efficacy study	Prospective, multi-center randomized, vehicle-controlled, double-masked	Patients 18 years of age and older undergoing cataract surgery	Loteprednol etabonate ophthalmic gel Vehicle	1-2 drops QID to study eye 1-2 drops QID to study eye	Approx. 14 days	406
577 Safety/ efficacy study	Prospective, multi-center randomized, vehicle-controlled, double-masked	Patients 18 years of age and older undergoing cataract surgery	Loteprednol etabonate ophthalmic gel Vehicle	1-2 drops QID to study eye 1-2 drops QID to study eye	Approx. 14 days	407

7.1.2 Categorization of Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as any adverse event (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.

AEs were collected from the time the subject gave informed consent until the last study visit or after, if needed. These included non-ocular AEs and ocular AEs for the study eye and untreated fellow eye prior and after rescue medication (RM) use.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooled data from Studies 576 and 577 was used in the analysis of common adverse events. Adverse events for each study were also evaluated individually.

7.2 Adequacy of Safety Assessments

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

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

7.2.2 Explorations for Dose Response

LE Gel was administered in one dose level (1 -2 drops four times a day for approximately 14 days) for each of the phase 3 studies. No dose response information was obtained.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with LE Gel.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, IOP, etc.) were adequately addressed in the design and conduct of the two clinical trials.

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 Gel 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, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, and ptosis.

See Section 7.4.5 for further detail.

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

Study 576 – Nonfatal SAEs

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 **sy**ncope 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 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) (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) (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. In the (b) (6), the 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.

Reviewer's Comments:

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

7.3.3 Dropouts and/or Discontinuations

	Study 576		Study 577	
Reason for Discontinuation	**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

Reviewer's Comments:

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

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in section 7.3.3. There were no other significant adverse events identified.

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 576 - Ocular Treatment-Emergent AEs in ≥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 ≥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 ≥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

Reviewer's Comments:

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

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/Clinical Trials

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
≥ 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

7.4.6 Immunogenicity

N/A – Immunogenicity testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

N/A – LE Gel does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

Key safety measures were analyzed stratifying by age (<65, =65< 75, and ≥75), gender, race (white and non-white). Based on the analyses by these subgroups, the events are consistent with the overall safety population.

7.5.4 Drug-Disease Interactions

No drug-disease interaction analyses were performed.

7.5.5 Drug-Drug Interactions

No drug interactions were reported in any clinical study involving LE Gel.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted

7.6.2 Human Reproduction and Pregnancy Data

No information was obtained on the use of LE Gel in these populations.

7.6.3 Pediatrics and Assessment of Effects on Growth

The clinical trials did not enroll any pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Based on postmarketing safety data collected through 31 Dec 2010 for LE as the active

pharmaceutical ingredient (including Lotemax suspension, Alrex, and Zylet), no case of overdose or substance-related disorder has been reported. There have been no reports of drug abuse, steroid abuse, or intentional drug misuse at the patient level.

7.7 Additional Submissions / Safety Issues

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

8 Postmarket Experience

Loteprednol etabonate is the active pharmaceutical ingredient in LE (b) (4) and is the same sterile form of the API that has been marketed in the following drug products:

- Lotemax - Loteprednol Etabonate Ophthalmic Suspension, 0.5%, marketed since March 1998
- Alrex - Loteprednol Etabonate Ophthalmic Suspension, 0.2%, marketed since March 1998
- Zylet - Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%, 0.3% launched December 2004
- Lotemax - Loteprednol Etabonate Ophthalmic Ointment, 0.5%, approved April 2011

In addition to the U.S., Lotemax, Alrex, and Zylet have been approved in countries throughout Latin America, Europe, and Asia/Pacific regions.

Quantities Shipped of Marketed Products

Product	Dates	Total Units (b) (6)
Lotemax	Mar 1998 – 31 Dec 2010	
Alrex	Mar 1998 – 31 Dec 2010	
Zylet	Dec 2004 – 31 Dec 2010	
Total		

There have been no Marketing Authorization withdrawals to date for Lotemax, Alrex, or Zylet.

9 Appendices

9.1 Literature Review/References

An independent literature review did not reveal any additional information relevant to this application. .

9.2 Labeling Recommendations

See labeling recommendations which follow in the attached label.

9.3 Advisory Committee Meeting

An advisory committee meeting was not required for this application.

9 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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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/

LUCIOUS LIM
09/27/2012

WILLIAM M BOYD
09/27/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202872 **Applicant:** Bausch & Lomb, Inc. **Stamp Date:** 11/29/2011

Drug Name: loteprednol etabonate ophthalmic gel 0.5% **NDA/BLA Type:** NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:		X		Evaluated 4 concentrations of loteprednol suspension (LE) & 2 dose frequencies (BID, QID) on LE 0.5%
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	X			Studies 576 & 577 for indication #1 (post-op inflam & pain). (b) (4)

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				(b) (4)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				Defer to stats
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				Defer to Stats
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Defer to stats
34.	Are all datasets to support the critical safety analyses available and complete?				Defer to stats
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes for indication #1 (b) (4)

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Lucious Lim	1/12/2012
Reviewing Medical Officer	Date
William Boyd	1/12/2012
Clinical Team Leader	Date

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

/s/

LUCIOUS LIM
02/28/2012

WILLIAM M BOYD
02/29/2012