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*APPLICATION NUMBER:*  
**200738Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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NDA:	200738
Submission Date(s):	22DEC2009
Brand Name	LOTEMAX
Generic Name	Loteprednol Etabonate Ophthalmic Ointment, 0.5%
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Bausch and Lomb, Inc.
Relevant IND(s)	IND 32,432
Submission Type; Code	Original NDA; 505(b)(1) application
Formulation; Strength(s)	Loteprednol etabonate ophthalmic ointment, 0.5%
Indication	Treatment of post-operative inflammation and pain following ocular surgery

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**TABLE OF CONTENTS**

<b>1. EXECUTIVE SUMMARY .....</b>	<b>2</b>
<b>1.1. RECOMMENDATION .....</b>	<b>2</b>
<b>1.2. PHASE IV COMMITMENTS .....</b>	<b>2</b>
<b>1.3. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS .....</b>	<b>2</b>
<b>2. QUESTION BASED REVIEW .....</b>	<b>4</b>
<b>2.1. GENERAL ATTRIBUTES OF THE DRUG .....</b>	<b>4</b>
<b>2.2. GENERAL CLINICAL PHARMACOLOGY .....</b>	<b>6</b>
<b>2.3. INTRINSIC FACTORS .....</b>	<b>8</b>
<b>2.4. EXTRINSIC FACTORS .....</b>	<b>8</b>
<b>2.5. GENERAL BIOPHARMACEUTICS .....</b>	<b>8</b>
<b>2.6. ANALYTICAL SECTION.....</b>	<b>9</b>
<b>3. LABELING RECOMMENDATIONS .....</b>	<b>10</b>

## **1. EXECUTIVE SUMMARY**

Loteprednol Etabonate Ophthalmic Ointment (LOTEMAX), 0.5% is a sterile, topical ophthalmic formulation of the active ingredient loteprednol etabonate, an anti-inflammatory corticosteroid. Loteprednol etabonate has been marketed in the United States since 1998 as Lotemax™ and Alrex™ ophthalmic suspensions and since 2005 in a fixed combination ophthalmic suspension with tobramycin as Zylet® (Loteprednol Etabonate 0.5% and Tobramycin 0.3% Ophthalmic Suspension). Loteprednol Etabonate Ophthalmic Ointment (LOTEMAX), 0.5% is proposed for the treatment of post-operative inflammation and pain following ocular surgery. The proposed dosage and route of administration for this indication are as follows: apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing throughout the first two weeks of the post-operative period.

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

### **1.1. Recommendation**

This application is acceptable from a clinical pharmacology perspective. No new clinical pharmacology data was presented in this application.

### **1.2. Phase IV Commitments**

No phase IV commitments are recommended.

### **1.3. Summary of Important Clinical Pharmacology Findings**

Loteprednol Etabonate Ophthalmic Ointment (LOTEMAX), 0.5% is a sterile, topical, anti-inflammatory corticosteroid for ophthalmic use. It is proposed for the treatment of post-operative inflammation and pain following ocular surgery. To support this indication, the applicant has conducted two adequate and well-controlled superiority studies of loteprednol etabonate ointment compared to vehicle for replicative evidence of safety and efficacy of the ointment formulation. Clinical pharmacokinetic studies were conducted during the development of Lotemax suspension and Zylet®, and these data have been submitted previously with the NDAs for these products (NDA #20-583 and #50-804, respectively). No new clinical pharmacology data was presented in this application. The pharmacokinetic data previously submitted addresses requirement for bioavailability outlined in 21 CFR 320.21. Thus, this application is acceptable from a clinical pharmacology perspective.

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Division of Clinical Pharmacology 4  
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Concurrence:

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Charles R. Bonapace, Pharm.D.  
Team Leader

cc:

Division File: NDA 200738

HFD-520 (CSO/Izadi)

HFD-520 (MO/Wadhwa)

HFD-520 (Chambers, Boyd)

HFD-880 (Lazor, Reynolds, Bonapace)

## 2. QUESTION BASED REVIEW

Since this submission is an original NDA for a drug product containing an active ingredient already approved in other locally administered ophthalmic drug products, only relevant questions from the OCP question-based review (QBR) are addressed below.

### 2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Loteprednol Etabonate Ophthalmic Ointment (LOTEMAX), 0.5% is a sterile, topical ophthalmic ointment formulation of the active ingredient loteprednol etabonate, an anti-inflammatory corticosteroid. The drug substance is (b) (4) containing mineral oil and white petrolatum. This formulation has been used in preclinical and clinical studies with the same qualitative and quantitative composition. No changes in formulation are intended for the commercial product. The chemical structure and physical-chemical properties of the active ingredient loteprednol etabonate are as follows:

**Structural Formula:**  $C_{24}H_{31}ClO_7$

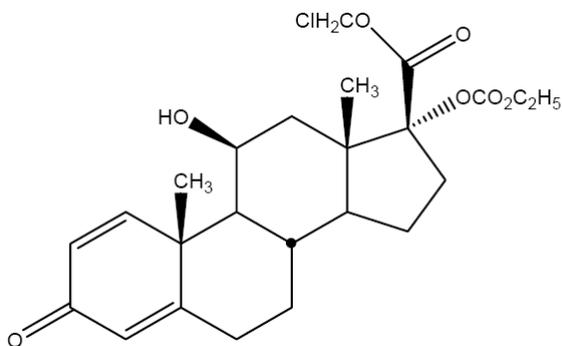
**USAN, INN:** loteprednol etabonate

**USP, Ph.Eur., JP:** Non-compendial

**CAS Registry Number :** 82034-46-6

**Chemical Name:** Chloromethyl 17 $\alpha$ -[(ethoxycarbonyl)oxy]- 11 $\beta$ -hydroxy-3-oxoandrosta-1,4-diene-17 $\beta$ -carboxylate

**Chemical Structure:**



**Molecular Weight:** 466.96

**Appearance:** White to off-white powder

**Solubility:**

Solvent	% Solubility (mg/100 mL solvent) (b) (4)

The drug product, Loteprednol Etabonate Ophthalmic Ointment, 0.5% is to be used for topical ophthalmic administration. The qualitative and quantitative composition of the drug product is provided in Table 2.1.1-1.

Table 2.1.1-1 Qualitative and Quantitative Composition of Loteprednol Etabonate Ophthalmic Ointment

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

Source: NDA 200738, section 2.3.P.1

*2.1.2. What is the proposed mechanism of drug action and therapeutic indication?*

Loteprednol etabonate is a corticosteroid. Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms such as induction and activation of lipocortin, induction of MAPK phosphatase 1 and repression of NF-κB-induced transcription of cyclooxygenase 2. Glucocorticoids can also inhibit NF-κB-mediated stimulation of the transcription of pro-inflammatory cytokines, chemokines, and cell adhesion molecules and complement factors.

Loteprednol Etabonate Ophthalmic Ointment (LOTEMAX), 0.5% is proposed for the treatment of post-operative inflammation and pain following ocular surgery.

*2.1.3. What is the proposed dosage and route of administration?*

The proposed dosage and route of administration are as follows: apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.

## 2.2. General Clinical Pharmacology

### 2.2.1. *What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?*

No new clinical pharmacology studies were submitted in this application. To support the (b) (4) the applicant has conducted two independent, randomized, multicenter, double-masked, parallel-group, vehicle-controlled safety and efficacy studies (Studies 525 and 526). The primary objective of these clinical studies was to compare the safety and efficacy of loteprednol etabonate ointment to its vehicle for the treatment of inflammation and pain following cataract surgery. For these studies, a total of 805 subjects were randomized at 33 investigative sites in the US. The safety population included 405 subjects treated with loteprednol etabonate ointment and 400 subjects treated with vehicle. Study duration was approximately four weeks from screening to the last visit. Randomized subjects self-administered approximately a ½ inch (1.3 cm) ribbon of study drug to the lower cul-de-sac of the study eye, QID at approximately four-hour intervals. Study treatment lasted approximately 14 days.

### 2.2.2. *What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?*

The hierarchical primary efficacy endpoints in each study were the proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8) followed by the proportion of subjects with Grade 0 (no) pain at Visit 5. Secondary endpoints included the proportion of subjects with complete resolution of anterior chamber cells and flare at each visit, as well as the change from baseline to each follow-up visit in anterior chamber cells and flare.

Previously, loteprednol etabonate suspension studies measured complete resolution of anterior chamber cells as a range of cells (0-5) and flare (none to trace). For the loteprednol etabonate ointment studies, a more conservative approach was taken, in that complete resolution of anterior chamber cells was defined as 0 cells and complete resolution of flare as none.

### 2.2.3. *Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?*

No pharmacokinetic data for Loteprednol Etabonate Ophthalmic Ointment, 0.5% was submitted in the current application.

### 2.2.4. *Exposure-Response*

#### 2.2.4.1. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

Treatment success in Studies 525 and 526 was defined as achieving complete resolution of cells and flare at Visit 5 (Postoperative Day 8), after approximately seven days of QID dosing. Superiority of loteprednol etabonate ointment to vehicle was demonstrated in both studies for the treatment of postoperative ocular inflammation and pain at Visit 5 for the ITT population

(Postoperative Day 8), as presented in Table 2.2.4.1-1. These results were further supported for both studies when the primary analyses were repeated using the PP population.

Table 2.2.4.1-1 Summary of Primary Efficacy Analysis - Studies 525 and 526 Combined

Endpoint	LE Ointment (N = 404)	Vehicle (N = 401)	Difference (95% CI) p-value
<b><i>Complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8)</i></b>			
<i>Yes</i>	112 (27.7%)	50 (12.5%)	15.3% (9.6%, 20.9%) p < 0.0001
<i>No</i>	292 (72.3%)	351 (87.5%)	
<b><i>Grade 0 (no) pain at Visit 5 (postoperative Day 8)</i></b>			
<i>Yes</i>	305 (75.5%)	173 (43.1%)	32.4% (25.7%, 39.0%) p < 0.0001
<i>No</i>	99 (24.5%)	228 (56.9%)	

A formal exposure/dose-response analysis for efficacy could not be conducted since only a single strength/dose of active treatment was studied in the clinical trials and no assessment of local or systemic concentrations of active drug were performed. For further discussion of the efficacy results, refer to the Medical Officer's and Biostatistician's reviews of this application.

*2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

Overall, 894 ocular treatment emergent adverse events (TEAEs) occurred prior to rescue medication use (313 and 581 TEAEs in the loteprednol etabonate ointment and vehicle treatment groups, respectively). The percentage of subjects who had at least one ocular TEAE in the study eye prior to rescue medication use in the loteprednol etabonate ointment treatment group (47.2%, 191) was significantly lower than those in the vehicle treatment group (78.0%, 312; p < 0.0001). The most prevalent ocular TEAEs that occurred at statistically different rates between treatment groups prior to rescue medication use included anterior chamber inflammation, eye pain, conjunctival hyperaemia, iritis, ciliary hyperaemia, lacrimation increased, and eye pruritus. In each case, the most prevalent ocular TEAEs occurred less frequently in the loteprednol etabonate treatment group.

It is important to note that anterior chamber inflammation and eye pain are signs/symptoms of the proposed indication for loteprednol etabonate ointment and may have occurred in the vehicle treatment group and not necessarily be an AE due to treatment. To address this issue, the applicant conducted a supplemental analysis which differentiated patients that had anterior chamber inflammation with actual worsening of scores for cells and flare versus patients with anterior chamber-related inflammation AEs recorded for rescue medication use where scores for cells and flare separately were stable or improved. This analysis characterized AEs related to safety as compared to AEs recorded as a requirement to initiate rescue medication. Results from this supplemental analysis showed that anterior chamber inflammation AE rates in the study eye prior to rescue medication use decreased in both treatment groups as compared to rates from the original analysis (original analysis: 27.2% [110] versus 50.0% [200] for Loteprednol Etabonate Ointment versus vehicle; supplemental analysis: 12.8% [52] versus 27.5% [110] for Loteprednol Etabonate Ointment versus vehicle, respectively).

A formal exposure/dose-response analysis for safety could not be conducted since only a single strength/dose of active treatment was studied in the clinical trials and no assessment of local or systemic concentrations of active drug were performed. An escalating dose-tolerance study was conducted during the development of Lotemax® (Loteprednol Etabonate Ophthalmic Suspension, 0.5%), Alrex® (Loteprednol Etabonate Ophthalmic Suspension, 0.2%), and Zylet® (Loteprednol Etabonate 0.5% and Tobramycin 0.3% Ophthalmic Suspension), and the data have been submitted previously with the NDAs for these products. Therefore, no dose-response studies were conducted by the sponsor for the Loteprednol Etabonate Ointment formulation. For further discussion of the safety results, refer to the Medical Officer's review of this application.

*2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

The dose and dosage regimen selected by the sponsor were based on and consistent with the approved dose and dosage regimen for Lotemax suspension for the treatment of postoperative inflammation (one to two drops four times daily (QID) for two weeks). The total daily dose of Lotemax is up to 2 mg/day (a 50 µL sized drop QID). Since approximately 90% of this amount would likely be lost due to spillage, nasolacrimal drainage, and blinking, the actual daily dose following administration of Lotemax suspension is approximately 200 µg/day. The maximum amount of ointment the human eye can accommodate is approximately 30 µg. Thus, the maximum daily dose of loteprednol following QID ointment application is approximately 150 µg/day, similar to that following suspension administration.

*2.2.5. What are the PK characteristics of the drug and its major metabolite?*

No clinical pharmacokinetic studies were conducted for the ointment formulation, and no new pharmacokinetic data was submitted in this application. Clinical pharmacokinetic studies were conducted during the development of Lotemax suspension and Zylet®, and these data have been submitted previously in the NDAs for these products (NDA #20-583 and #50-804, respectively). Because pharmacokinetic data from the marketed products are available and the ointment is not expected to produce higher systemic exposure than the suspension products (see Section 2.2.4.3), the current application for Loteprednol Etabonate Ophthalmic Suspension, 0.5% is acceptable from a clinical pharmacology perspective.

For further information on the pharmacokinetic characteristics of loteprednol etabonate, specifically systemic availability following ocular administration, please refer to the Office of Clinical Pharmacology review (by Dr. Ene Ette dated November 3, 1995) and the Medical Officer's review (by Dr. Wiley Chambers dated November 16, 1995) of the original NDA #20-583 for Lotemax Ophthalmic Suspension.

**2.3. Intrinsic Factors**

Not applicable.

**2.4. Extrinsic Factors**

Not applicable.

**2.5. General Biopharmaceutics**

Not applicable.

**2.6. Analytical Section**  
Not applicable.

### 3. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling (recommendations appear in ***bold italicized underlined type***).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms (b) (4)

### 12.3 Pharmacokinetics

The systemic exposure to loteprednol etabonate following ocular administration of LOTEMAX ointment has not been studied in humans. However, results from a bioavailability study with LOTEMAX suspension in normal volunteers established that plasma (b) (4) ***concentrations*** of loteprednol etabonate and  $\Delta^1$  cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate suspension, 8 times daily for 2 days or 4 times daily for 42 days. ***The maximum systemic exposure to loteprednol following administration of the ointment product dosed four times daily is not expected to exceed exposures attained with LOTEMAX suspension dosed up to two drops four times daily.***

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200738	ORIG-1	BAUSCH AND LOMB INC	LOTEPREDNOL ETABONATE OINTMENT, 0.5%

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KIMBERLY L BERGMAN  
08/20/2010

CHARLES R BONAPACE  
08/20/2010

## CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 200738  
 Drug Name: Lotemax (loteprednol etabonate ophthalmic ointment, 0.5%)  
 Applicant: Bausch and Lomb  
 Submission Date: 22DEC2009  
 Filing Date: 21FEB2010  
 PDUFA Date: 23OCT2010  
 OCP Primary Reviewer: Kimberly L. Bergman, PharmD  
 OCP Team Leader: Charles Bonapace, PharmD

<i>QUESTION</i>	<i>YES</i>	<i>NO</i>	<i>NA</i>	<i>COMMENTS</i>
<b><i>Fileability:</i></b> <b><i>Is the Clinical Pharmacology section of the application fileable?</i></b> <b><i>(if 'NO', please comment as to why it is not fileable)</i></b>	<b><i>X</i></b>			
<i>Fileability Review Components</i>				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No new clinical pharmacology studies were submitted with this application.
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No changes in formulation are intended for the commercial product.
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

\_\_\_\_\_  
OCP Primary Reviewer

\_\_\_\_\_  
Date

\_\_\_\_\_  
OCP Team Leader

\_\_\_\_\_  
Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200738	ORIG-1	BAUSCH AND LOMB INC	LOTEPREDNOL ETABONATE OINTMENT, 0.5%

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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.**

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/s/

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01/29/2010

CHARLES R BONAPACE  
01/29/2010