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RESEARCH**

APPLICATION NUMBER:
202872Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA:	202-872 (N-000)
Submission Date:	29 November 2011; 20 January 2012
Drug Product:	Loteprednol etabonate ophthalmic gel, 0.5%
Trade Name:	TRADENAME
Sponsor:	Bausch & Lomb
Submission Type:	Original NDA submission; Amendment
OCP Reviewer:	Gerlie Gieser, PhD
Team Leader:	Philip Colangelo, PharmD, PhD

Table of Contents

<i>I. Executive Summary</i>	1
<i>A. Recommendations</i>	1
<i>B. Phase IV Commitments</i>	1
<i>C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings</i>	1
<i>II. Question-Based Review</i>	3
<i>III. Detailed Labeling Recommendations</i>	5
<i>IV. Appendices</i>	6
<i>A. Proposed Package Insert</i>	6
<i>B. Cover Sheet and OCP Filing/Review Form</i>	11

I. Executive Summary

A. Recommendations

From a Clinical Pharmacology perspective, the information contained in this NDA submission is acceptable provided satisfactory agreement is reached between the sponsor and the FDA regarding the language in the package insert.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor is seeking approval of TRADENAME (loteprednol etabonate, LE) ophthalmic gel, 0.5% for the treatment of inflammation and pain following ocular surgery based on the positive efficacy and safety findings of two adequate and well-controlled trials. The proposed dosing regimen (1 to 2 drops to the eye four times daily) was evaluated in the clinical trials conducted. Previously, Lotemax® (LE) ophthalmic suspension 0.5% and Lotemax® ophthalmic ointment 0.5% were approved by the FDA for the same indication.

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

(b) (4)

(b) (4)

Gerlie Gieser, Ph.D.
Office Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL) _____

II. Question-Based Review

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Lotemax® (loteprednol etabonate; LE) 0.5% ophthalmic *suspension* was approved in 1998 for the treatment of inflammation and pain following ocular surgery, as well as for the treatment of steroid-responsive inflammatory conditions. Following multiple doses (i.e., 1- 2 drops QID for 43 days) of Lotemax® suspension, systemic LE concentrations were below the limit of assay quantification (<1 ng/mL) at all sampling timepoints in healthy subjects. Lotemax® ophthalmic *ointment* is also marketed for the treatment of inflammation and pain following ocular surgery; no clinical pharmacokinetic studies were conducted specifically with the ointment. In rabbits, nonquantifiable (<0.1 ng/mL) systemic LE exposures up to 24 hours post-instillation of single doses of the ophthalmic suspension and the ophthalmic ointment were reported.

The sponsor developed TRADENAME (loteprednol etabonate; LE) *gel* 0.5% to (b) (4) allowing for uniform dosing of LE when the product is squeezed through the tip of the bottle and eventually transformed to the liquid (suspension) state. No clinical pharmacokinetic studies were conducted specifically with the proposed LE gel formulation. Given that in a rabbit PK study (BL1101), maximal mean systemic LE concentrations were approximately 7.3 ng/mL (range: 2 to 17 ng/mL) at 1.5 hours post-dose which declined to < 0.1 ng/mL by 6 h following single topical ocular dosing with the LE gel 0.5%, it is reasonable to assume that ocular dosing with the proposed LE ophthalmic gel 0.5% would produce systemic LE exposure in humans that is low and likely not clinically significant. It is noted that in the Phase 3 trials, the incidence of non-ocular adverse events was not statistically significantly different between TRADENAME LE Gel 0.5% and the placebo control.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Loteprednol etabonate (LE) is an anti-inflammatory corticosteroid and an analogue of prednisolone. Lotemax® (LE) ophthalmic suspension and ointment have been marketed in the USA since 1998 and 2011, respectively.

According to the sponsor's description, TRADENAME (loteprednol etabonate) ophthalmic gel 0.5% is (b) (4)

(b) (4)

3. What are the proposed dosage(s) and route(s) of administration?

As with the approved Lotemax® (LE) ophthalmic suspension 0.5%, the recommended dosage of TRADENAME (LE) ophthalmic gel 0.5% for the treatment of inflammation and pain following ocular surgery is one to two drops into the conjunctival sac of the affected eye(s) four times daily after surgery and continuing throughout the first 2 weeks of the post-operative period.

4. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There were no Clinical Pharmacokinetics studies conducted specifically with the proposed loteprednol etabonate (LE) 0.5% gel formulation although the NDA submission referenced the systemic PK and aqueous humor PK studies previously conducted with the already approved LE (as Lotemax®) ophthalmic suspension 0.5%. The plasma and aqueous humor PK data obtained from such studies were previously reviewed by Dr. Enne Ette (Clinical Pharmacology reviewer of the Lotemax® original NDA submission).

To support the approval of TRADENAME (loteprednol etabonate) ophthalmic gel 0.5% for the treatment of inflammation and pain following ocular surgery, two Phase 3 clinical trials were conducted. Both trials were randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies in 813 subjects with a protocol-specified threshold amount of anterior chamber cells. TRADENAME was more effective compared to its vehicle for treatment of post-operative inflammation and pain following cataract surgery. The primary endpoints were complete resolution of anterior chamber cells (cell count of 0) and no pain at postoperative day 8. In both studies, the sponsor's proposed dosing regimen was evaluated for efficacy and safety.

5. What is the status of pediatric studies and/or any pediatric plan for study?

The PREA requirement was fulfilled for loteprednol etabonate by the sponsor in relation to the application and approval of Lotemax® ophthalmic suspension 0.5%. (b) (4)

III. Detailed Labeling Recommendations
(Reviewer's deleted text = strikethrough)

12.3 Pharmacokinetics

...

The systemic exposure to loteprednol etabonate following ocular administration of TRADENAME has not been studied in humans. ~~However, results from a bioavailability study with LOTEMAX® suspension in normal volunteers established that plasma concentrations of loteprednol etabonate and Δ^1 -corticene 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, 8 times daily for 2 days or 4 times daily for 42 days. The maximum systemic exposure to loteprednol etabonate following administration of the gel product dosed 4 times daily is not expected to exceed the exposure attained with LOTEMAX® suspension dosed up to two drops 4 times daily.~~

B. Cover Sheet and OCP Filing/Review Form

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ESG

Re: NDA 202872 - (b)(4) loteprednol etabonate ophthalmic gel, 0.5%
Sequence 0002: Original New Drug Application

Dear Dr Albrecht:

Pursuant to 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Bausch & Lomb, Incorporated submits this original New Drug Application (NDA) for (b)(4) (loteprednol etabonate ophthalmic gel, 0.5%). This NDA provides for substantial evidence of safety and efficacy for the use of (b)(4) (loteprednol etabonate ophthalmic gel, 0.5%) as per the proposed labeling presented in Section 1.14.1.2:

- (b)(4) is a topical gel and is indicated for the treatment of inflammation and pain following ocular surgery.
- (b)(4)

The following information contained in this submission will permit the Agency to make a knowledgeable judgment for the proposed indication (b)(4)

- Two phase 3, adequate and well controlled clinical trials conducted with loteprednol etabonate ophthalmic gel, 0.5% versus formulation vehicle (placebo). These two studies provide safety and efficacy data for the use of (b)(4) for the treatment of inflammation and pain following ocular surgery indication.
 - Investigator Financial Certification and Disclosure documents are included in Section 1.3.4, as appropriate.
- Clinical studies conducted with the use of the same active ingredient, loteprednol etabonate (LE), in various topical formulations previously approved for ocular indications such as Seasonal Allergic Conjunctivitis, ocular bacterial infection response to steroids, post-operative treatment of pain and inflammation after ocular surgery, are summarized and appraised. The consolidated efficacy and safety data in its totality provide evidence for the safe and effective use of (b)(4) for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior

Appears This Way On Original

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202872	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	III	Generic Name	Loteprednol etabonate
Medical Division	DTOP	Drug Class	
OCP Reviewer	Gerlie Gieser, PhD	Indication(s)	Treatment of inflammation & pain in the eye
OCP Team Leader	Philip Colangelo, PharmD, PhD	Dosage Form	Ophthalmic gel, 0.5%
Pharmacometrics Reviewer	-	Dosing Regimen	1-2 gts 4x daily
Date of Submission	29 November 2011	Route of Administration	topical
Estimated Due Date of OCP Review	~04 August 2012	Sponsor	Bausch + Lomb
Medical Division Due Date	~11 August 2012	Priority Classification	
PDUFA Due Date	29 September 2012		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	x	2		plasma; used Lotemax® ophth suspension (not gel)
Patients-				
single dose:	x	2		aqueous humor; used Lotemax® ophthalmic suspension (not gel)
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?	x			Dosing regimen evaluated in two Ph 3 trials
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate	x			

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewer's Note regarding proposed USPI -12.3 Pharmacokinetics (not to be sent to the sponsor): Since the human plasma and aqueous humor PK of the ophthalmic gel formulation were not studied specifically, the (b) (4) US Package Insert will simply state that fact, and not describe theoretical

systemic exposures relative to that following administration of the approved Lotemax® ophthalmic suspension. The animal PK information available for [REDACTED]^{(b)(4)} and the human PK information available for Lotemax® will be considered by the reviewer in understanding the observed efficacy and safety profiles of [REDACTED]^{(b)(4)} from a Clinical Pharmacology perspective.

Gerlie Gieser, Ph.D. (signed)

12/22/2011

Reviewing Clinical Pharmacologist

Date

Philip Colangelo, PharmD, PhD (signed)

Team Leader

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

/s/

GERLIE GIESER
05/17/2012

PHILIP M COLANGELO
05/17/2012