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APPLICATION NUMBER:
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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 202872
Supporting document/s: 000
Applicant's letter date: 11/29/11
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Product: Loteprednol etabonate ophthalmic gel, 0.5%
Indication: Inflammation and pain following ocular surgery
Applicant: Bausch and Lomb, Inc
Review Division: CDER/OAP/Division of Anti-Infective and
Ophthalmology Products
Reviewer: Robeena Aziz, MPH, PhD
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Project Manager: June Germain

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1 Executive Summary

1.1 Introduction

The sponsor (Bausch and Lomb) is submitting this NDA for the reformulation of loteprednol etabonate ophthalmic gel, 0.5%. The proposed formulated gel is indicated for treatment of inflammation and pain following ocular surgery. Patients will be dosed 1-2 drops into the conjunctival sac of the affected eye(s) 4x/daily after surgery and continuing throughout the first 2 weeks of the post-operative period. Loteprednol etabonate, or may be referred as LE throughout this review, is a glucocorticoid compound having anti-inflammatory properties and has been used (and approved) for treating ocular inflammatory disorders and is the active ingredient in this gel formulation. Most of the preliminary nonclinical information to support this NDA application is referenced to FDA approved products such as Lotemax® (NDAs 20583), Lotemax ointment® (NDA 200738), Zylet® (NDAs (b) (4) and NDA 50804), and Alrex® (NDA 20803), which contain the active ingredient, loteprednol etabonate but in a suspension and/or ointment form. Additional nonclinical studies to support the current gel formulation were reviewed by Dr. Conrad H. Chen, PhD. under IND 102 654.

The proposed drug is a sterile polycarbophil-based gel which is similar in efficacy to the currently approved products, but the gel provides additional benefits such as (b) (4)

The clinical safety and efficacy of the active ingredient in the gel, loteprednol etabonate, has been extensively evaluated in other FDA approved products mentioned above.

1.2 Brief Discussion of Nonclinical Findings

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

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

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

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

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

Table 2: Formulations of LE ophthalmic gel (polycarbophil) used in the GLP ocular nonclinical safety studies

Description	0.7% w/w LE Polycarbophil Gel	0.4% w/w LE Polycarbophil Gel	Vehicle for LE Polycarbophil Gel			
Lot Number(s)	2593-YH-160-7 2593-YH-201-7	2593-YH-160-4 2593-YH-201-7	2593-YH-160-0			
Loteprednol etabonate	4 mg/g	7 mg/g	0 mg/g			
Edetate disodium dihydrate, USP	(b) (4)					
Glycerin, USP						
Propylene Glycol, USP						
Boric Acid NF						
Polycarbophil, USP						
Sodium chloride, USP						
Tyloxapol, USP						
Sodium hydroxide, (b) (4)						
Benzalkonium chloride solution, (b) (4) EP/USP						
Water for Injection, USP						
Total				1000	1000	1000

Note: The composition in this table is based on the concentration of the components of the formulation, not of the hydrate salts used to prepare the formulation. All numbers in the table are listed as mg/g.

The following lists a summary of nonclinical findings. Please see IND 102654 reviewed by Dr. Conrad Chen for a comprehensive detailed review of these studies.

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

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

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

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

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

1.3 Recommendations

1.3.1 Approvability

From a pharmacology/toxicology perspective, approval is recommended.

1.3.2 Additional Non Clinical Recommendations

No additional non clinical comments and/or recommendations.

1.3.3 Labeling

For all nonclinical sections of the label i.e. mechanism of action, pregnancy category, nursing mothers, women of childbearing potential, genetic and reproductive toxicology, the proposed labeling is proposed to be similar to that of loteprednol etabonate ophthalmic suspension 0.5% (Lotemax® - NDA 20853) and loteprednol etabonate ophthalmic ointment, 0.5% (Lotemax®- NDA 200738).

2 Drug Information

2.1 Drug: Loteprednol etabonate ophthalmic gel 0.5%

CAS Registry Number (Optional): 82034-46-6

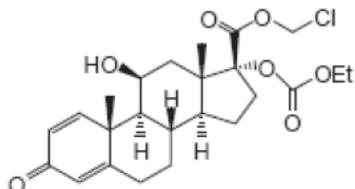
Generic Name: Loteprednol etabonate (LE)

Code Name: P-5604, OPC-5604, HGP-1, BOL-303011-X

Chemical Name: Androsta-1, 4-diene-17-carboxylic acid, 17- [(ethoxycarbonyl)oxy]-11-hydroxy-3-Oxo, chloromethyl ester, (11β, 17a)

Molecular Formula/Molecular Weight: C₂₄H₃₁ClO₇/467 g/mole

Structure or Biochemical Description



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs and NDAs

IND/NDA number	Description of submission	Indication	Approval date
INDs			
IND 32 432	0.5% loteprednol etabonate (LE) ointment/suspension	Ophthalmic steroidal anti-inflammatory disease	N/A
IND 102 654	loteprednol etabonate (LE) ophthalmic gel drop 0.5%.	Treatment of post-operative inflammation and pain following ocular surgery	N/A. IND was submitted on 9/30/09
NDAs			
NDA 20 583 – Lotemax®	loteprednol etabonate (LE) ophthalmic suspension 0.5%	Ophthalmic inflammation and allergic conditions	March 1998
(b) (4)			
NDA 50 804 – Zylet®	Loteprednol etabonate (LE) 0.5% and tobramycin 0.3% suspension. See Note below.	Indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial	Dec. 2004

		ocular infection exists	
NDA 20 803 – Alrex®	Loteprednol etabonate (LE) suspension 0.2%	Treatment of signs and symptoms of seasonal allergic conditions	March 1998
NDA 200 738 Lotemax®	Loteprednol etabonate (LE) ophthalmic ointment 0.5%	Treatment of post-operative inflammation and pain following ocular surgery	April 2011

(b) (4)

2.3 Drug Formulation

The gel contains 5 mg/g loteprednol etabonate as a preserved ophthalmic gel. Loteprednol etabonate is the active pharmaceutical ingredient (API) and is the same sterile form of the API that has been approved and marketed for over a decade in approved products. Table 3 lists the composition of loteprednol etabonate gel, 0.5%.

Table 3: Qualitative and quantitative composition of loteprednol etabonate ophthalmic gel drop, 0.5%

Component	Function	Concentration	
		mg/g*	%w/w*
Loteprednol Etabonate	Active	5.00	0.500
Edetate Disodium Dihydrate, USP			
Glycerin, USP			
Propylene Glycol, USP			
Boric Acid, NF			
Polycarbophil, USP			
Sodium Chloride, USP			
Purified Water, USP			
Tyloxapol, USP			
Sodium Hydroxide (b) (4)			
Benzalkonium Chloride Solution, (b) (4) USP			

* composition will be converted to industry standard weight/volume when additional density information is available

† label claim for BAK is 30 ppm or 0.003%

2.4 Comments on Novel Excipients

The inactive ingredients in the formulations are within the limits of previously approved ophthalmic drug products (CDER Inactive Ingredient Search for Approved Drug Products). The drug product named 0.5% LE Ophthalmic Gel is the same product previously named as 0.4% LE Ophthalmic Suspension except for the LE content (see Memo for Pre-IND Meeting dated August 4, 2008 by Dr. Conrad Chen, PhD). Another

difference between the formulations is the content of preservative benzalkonium chloride (b) (4) in gel vs. 0.1% in previously approved products).

2.5 Comments on Impurities/Degradants of Concern

There are no pharmacology/toxicology concerns. The acceptance criteria for most specified impurities are set at or lower than 0.5%, which is the identification threshold according ICH Q3B. The acceptance criteria for (b) (4) are set at (b) (4) levels (b) (4).

2.6 Proposed Clinical Population and Dosing Regimen

Apply one or two drops into the conjunctival sac of the affected eye(s) 4x/daily after surgery and continuing throughout the first 2 weeks of the post-operative period.

2.7 Regulatory Background

- A Pre-IND meeting was held on 8/4/08
- An IND was submitted on 9/30/09
- An EOP-2 meeting was held on 8/26/09
- A preNDA meeting was held on 4/29/11

3 Studies Submitted

3.1 Studies Reviewed

One pharmacokinetic distribution study (see below) was reviewed in the current submission. All other studies were reviewed under previous INDs and NDAs listed in Section 2.2 – Relevant INDs and NDAs.

Study Title	Study No.	Module
Investigation of the ocular and systemic pharmacokinetics of loteprednol etabonate (0.5%) in a gel formulation following a single topical ocular administration to Dutch Belted Rabbits	BL11001	4.2.2.3

3.2 Studies Not Reviewed

All were reviewed under the relevant INDs and NDAs.

3.3 Previous Reviews Referenced

Please see Section 2.2 - Relevant INDs and NDAs above

4 Pharmacology

4.1 Primary Pharmacology

Since the ocular and systemic pharmacology of the active pharmaceutical ingredient, loteprednol etabonate (LE), was reviewed as part of the development of Lotemax® NDA 20 583, no additional primary pharmacology studies were needed to support the LE gel

formulation. The completed primary and secondary pharmacology studies were intended to provide proof-of-concept for the drug. Most of these nonclinical pharmacology studies were conducted several years ago at research/academic institutions, therefore, the available raw data and study findings are submitted to the sponsor as abbreviated summary reports and/or literature citations.

In general, primary pharmacology studies showed that loteprednol etabonate is a corticosteroid compound with similar activity to dexamethasone (DEX) and betamethasone-17-valerate (BMV) and similar anti-inflammatory effectiveness to prednisolone acetate (PA) at the 1% concentration.

Receptor binding studies show that LE has 4.3 times greater binding affinity than DEX for glucocorticoid (Type II) receptors, and that LE binds competitively to transcortin, a corticosteroid-binding plasma protein. There are two major metabolites of loteprednol etabonate are PJ-91 and PJ-90. Both metabolites were shown not to bind to the glucocorticoid receptor indicating that there is systemic absorption of the parent molecule and not its metabolites.

4.2 Secondary Pharmacology

No additional secondary pharmacology studies were needed to support the loteprednol etabonate gel formulation. The following information was excerpted from NDA 200783.

“Secondary pharmacology effects have been studied with LE in *in vitro* and *in vivo* models. In these studies, LE was evaluated for a potential effect on corneal wound healing and scar formation (*in vitro* and *in vivo*), intraocular pressure (*in vivo*), skin thickness and thymus weight (*in vivo*). As with other corticosteroids, LE decreased scar formation, inhibited inflammatory cell infiltration, inhibited fibroblast proliferation, and decreased tensile strength of the resulting scar. No clear effect on intraocular pressure was noted with LE. Topical ocular treatment of normotensive rabbits with LE (0.1%, 1 dose per hour for 7 hours on two consecutive days) did not result in a sustained rise in IOP during the 55-h interval following the first administration”.

4.3 Safety Pharmacology

Safety pharmacology studies were not conducted with loteprednol etabonate as part of the development of Lotemax®. Safety pharmacology studies at this stage in development are not necessary to support the loteprednol etabonate gel formulation since a vast amount of clinical experience with loteprednol etabonate did not report any adverse or significant risk.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The Sponsor referred to previously referred NDA 20583 to access the initial pharmacokinetics of loteprednol etabonate. To support the loteprednol etabonate gel formulation, three *in vivo* ocular PK distribution studies were conducted. Two ocular PK studies were conducted to characterize the ocular pharmacokinetics of loteprednol

etabonate at a range of concentrations (0.2%, 0.4%, 0.6%, and 1%) in a polycarbophil-based gel. These studies were reviewed by Dr. Conrad Chen, PhD under IND 102654 and discussed in EOP2 meeting minutes on Aug. 12, 2009. The third study, investigated the ocular and systemic pharmacokinetics of loteprednol etabonate (LE, 0.5%) in a gel formulation following a single topical ocular administration. The third study is reviewed in detail below. Dutch Belted rabbits were used in all studies.

In the first study (Study No. BL08009), loteprednol etabonate was prepared in the polycarbophil-based gel formulation at target loteprednol etabonate concentrations of 0.2%, 0.6%, and 1%. In the second study (Study No. BL08010), animals received either the polycarbophil formulation with 0.4% loteprednol etabonate, or Lotemax (0.5% LE suspension). Results from these studies were compared with the results from a previous study (Study No. BL07012), in which rabbits received Alex (0.2% LE suspension). Animals received a single topical instillation (50 μ L) of the appropriate formulation into each eye. At predetermined intervals through 24 h after dosing, 4 rabbits per collection time were euthanized for each treatment group and samples of plasma, tear fluid, aqueous humor, conjunctiva, and cornea were obtained for analysis. Concentrations of loteprednol etabonate were measured using LC/MS/MS methods.

The results showed that the polycarbophil-based formulation afforded somewhat higher ocular exposure (1.2 to 3 fold higher in terms of AUC and C_{max}) in tear and conjunctiva but the exposure in cornea and aqueous humor was similar to the marketed products. According to the sponsor, the systemic exposure to loteprednol etabonate following ocular administration of the polycarbophil-based formulation was low consistent with that observed with the Lotemax formulation. The plasma loteprednol etabonate concentrations were < 1 ng/mL in most animals. Table 4 outlines the results of this study.

In the third study (Study No. BL11001), animals received a 35- μ L instillation of loteprednol etabonate in the gel formulation at a concentration of 0.5%, the concentration used in the clinical trials. The gel formulation resembled that used in the previous ocular PK studies except the benzalkonium chloride (BAK) concentration in this study was decreased to 30ppm instead of 50ppm (used in the other studies) in order to match the final formulation used in clinical trials. The concentration of LE was measured using LC/MS/MS methods and non-compartmental methods were used for the pharmacokinetic analysis of the concentration versus time data. Following a single 175- μ g dose, loteprednol etabonate was rapidly absorbed and widely distributed, with maximum concentrations observed within 30 min. in ocular tissues and within 1.5 h in plasma. There was a large inter-animal variability in exposure to loteprednol etabonate. Minimal loteprednol etabonate concentrations were observed in ocular tissues within 5 min after dosing. The highest concentrations of loteprednol etabonate were observed in conjunctiva, cornea, iris/ciliary body, and aqueous humor (concentrations = 4.03 μ g/g, 2.18 μ g/g, 0.162 μ g/g, and 0.0138 μ g/mL respectively). The concentration of loteprednol etabonate in tissues was still present at 12-h after a single dose. There was low systemic exposure to loteprednol etabonate with a maximal concentration of 7.3 ng/mL in the plasma (Table 6). A detailed review of the study is discussed below.

Table 4: Pharmacokinetic parameter values for loteprednol etabonate following a single topical ocular administration to pigmented rabbits

Formulation	Dose	Tissue/Matrix	C _{max} ^a (µg/g)	AUC(0-t) (µg ^h /g)
Polycarbophil-based Gel Formulation	0.1 mg/eye (0.2%) ^c	Tear	1120 ± 337	594
		Conjunctiva	6.96 ± 6.00	29.6
		Cornea	1.11 ± 0.570	4.20
		Aq. Humor ^b	0.0137 ± 0.0120	0.0248
	0.2 mg/eye (0.4%) ^d	Tear	1050 ± 1060	802
		Conjunctiva	14.6 ± 15.9	75.8
		Cornea	2.09 ± 0.438	9.77
		Aq. Humor ^b	0.0157 ± 0.00395	0.0317
	0.3 mg/eye (0.6%) ^c	Tear	2780 ± 707	1590
		Conjunctiva	13.8 ± 5.46	69.8
		Cornea	2.50 ± 1.51	7.87
		Aq. Humor ^b	0.0173 ± 0.00340	0.0404
0.5 mg/eye (1%) ^c	Tear	2800 ± 1500	1490	
	Conjunctiva	18.5 ± 15.5	107	
	Cornea	2.74 ± 1.53	12.3	
	Aq. Humor ^b	0.0191 ± 0.00876	0.0438	
Lotemax® Formulation	0.25 mg/eye (0.5%) ^d	Tear	847 ± 1030	452
		Conjunctiva	12.5 ± 13.9	25.4
		Cornea	1.23 ± 1.01	3.97
		Aq. Humor ^b	0.00937 ± 0.00698	0.0192
Alrex® Formulation	0.1 mg/eye (0.2%) ^e	Tear	433 ± 444	276
		Conjunctiva	2.45 ± 1.59	22.8
		Cornea	1.46 ± 0.422	4.02
		Aq. Humor ^b	0.0128 ± 0.00462	0.0237

^a C_{max} values represent maximum mean ± SD LE concentration

^b Relevant units for aqueous humor are µg/mL for C_{max} and µg^h/mL for AUC(0-t)

^c Data from BL08009

^d Data from BL08010

^e Data from BL07012

BL11001: Investigation of the ocular and systemic pharmacokinetics of loteprednol etabonate (0.5%) in a gel formulation following a single topical ocular administration to Dutch Belted Rabbits

Key Study Findings:

- Summary of findings are listed in Table 6 below.
- The highest concentrations of loteprednol etabonate were present in the tear fluid followed by bulbar conjunctiva, cornea, iris/ciliary body, and aqueous humor, based on C_{max} and AUC values.
- Loteprednol etabonate was rapidly absorbed and widely distributed with maximum concentrations achieved at 0.5 h in ocular tissues and 1.5 h in the plasma.
- There was large inter-animal variability in all ocular tissues, particularly for tear fluid and bulbar conjunctiva samples.
- Measurable concentrations of loteprednol etabonate were present in all ocular tissues throughout the 24-h sampling period, with the exception of aqueous humor, where measurable levels were observed through only 12 h after dosing.

Best Available Copy

- Measurable concentrations were detected in the plasma of all animals in the 24-h sampling subgroup.

Report #:

BL11001

Conducting Laboratory and Location:

(b) (4)

Date of Study Initiation

9/29/11

GLP Compliance

No

QA Report

Yes (), No (x)

Drug and lot #

loteprednol etabonate ophthalmic gel (0.5%); 537591

Doses:

single dose 175- μ L dose using topical ocular instillation – 35 μ L/eye

Species/strain:

Rabbits / Dutch Belted (pigmented)

Number/sex/group or time point:

40 males

Route; formulation; volume; and infusion rate:

Topical ocular instillation; LE polycarbophil-based gel, 0.5% (using 30 ppm benzalkonium chloride (BAK) – See Table 5 below)

Age:

4 months age

Weight:

2 kg

Parameters:

- Ocular tissue samples were collected at 5 min, 15 min, 30 min, 1, 2, 4, 6, 8, 12 and 24 hrs after dosing.
- At predetermined time intervals (see above for specific times), animals (n=4/collection time) were euthanized and selected ocular tissues (tear fluid, bulbar conjunctiva, cornea, aqueous humor, and iris/ciliary body) and plasma samples were collected.
- In addition, blood samples (~1 mL) were collected from the central ear artery from the 24-h sampling subgroup
- Concentrations of LE in ocular tissues and plasma were determined by LC/MS/MS.

Table 5: Formulation of loteprednol etabonate ophthalmic gel, 0.5%

Loteprednol Etabonate Ophthalmic Gel, 0.5%	
Lot Number	537591
API Concentration [measured by LC] (mg/mL)	5.01
pH	6.5
Osmolality (mOsm/kg)	275
Viscosity (cps)	1225
Benzalkonium Chloride (%)	0.003

Table 6: Pharmacokinetic parameter values for LE following single topical ocular administration of LE gel (0.5%) to pigmented rabbits

Tissue/Matrix	C _{max} (µg/g)	T _{max} (h)	AUC _(0-t) (µg*h/g)
Tear Fluid	1560 ± 1420	0.25	872
Bulbar Conjunctiva	4.03 ± 2.42	0.0833	18.2
Cornea	2.18 ± 0.685	0.0833	5.44
Aqueous Humor	0.0138 ± 0.00604	0.5	0.0157
Iris/Ciliary Body	0.162 ± 0.0384	0.5	0.282
Plasma	7.30 ± 6.79 ng/mL	1.5 ^a	6.77 ± 4.62 ^b ng*h/mL

Abbreviations: C_{max}: Maximum mean (± SD) concentration observed after dosing; T_{max}: time C_{max} was observed; AUC_(0-t): area under the concentration versus time curve from the time of dosing through time (t) of the last measurable concentration.

Note: For aqueous humor, the relevant units for C_{max} and AUC are µg/mL and µg*h/mL, respectively.

^a Plasma T_{max} represents median value from 4 animals.

^b Plasma C_{max} and AUC estimates represent the mean (± SD) value from 4 animals.

[Tables excerpted from Sponsor's submission]

6 General Toxicology

6.1 Single-Dose Toxicity

No additional studies were needed. Single dose studies for the initial development of loteprednol etabonate were submitted as part of NDA 20-583.

6.2 Repeat-Dose Toxicity

Repeat dose studies for the initial development of loteprednol etabonate were submitted as part of NDA 20583, with additional studies submitted under NDA 50804 and NDA 200738.

To support the development and registration of the loteprednol etabonate gel formulation, the sponsor conducted a bridging GLP repeat dose 28-day ocular toxicity study in rabbits followed by a repeat dose 29-day toxicokinetic study. Both studies were

reviewed in detail by Dr. Conrad Chen, PhD under IND 102 654. A quick synopsis of key study findings excerpted from this IND is presented below.

In the 28-day ocular study, two concentrations of loteprednol etabonate (0.4 and 0.7%, 50 µL drop size) in polycarbophil suspension or the vehicle are administered by ocular instillation to rabbits (N= 3-5 animals/sex/group) 4x/day for 28 days. The contralateral eye serves as a vehicle control for the 0.4% and 0.7% dose groups and as an untreated control in the vehicle control group. There were no significant ocular findings during the course of the study and the ocular NOAEL was 0.7%. Decrease in actively growing hair follicles, evident in both the eyelids of treated animals, was observed; the eyelashes and meibomian glands were not affected. This was concluded to be related to a dermal exposure to the test article during dosing and is consistent with the known steroid modulation of their follicle cycling. Systemically, there were decreases in absolute and relative adrenal weights with a histopathologic correlate of cortical atrophy observed. The systemic NOAEL was less than 0.4% LE based on body cortical atrophy of the adrenal glands.

In the 29-day TK study, two concentrations of LE gel (0.4 and 0.7%) were administered topically to one eye of rabbits (N=4 females/group) 4x/day for 27 consecutive days. Systemic exposure to loteprednol etabonate after topical ocular dosing was confirmed. After the 4th dose on Day 1, there was an increase in systemic exposure with increased dose concentration from 0.4% to 0.7%. The increase in Cmax was less than dose proportional, but the increase in AUC was approximately dose proportional. On Day 27, the increase in dose concentration did not result in an increase in Cmax or AUC, and no accumulation of LE was observed between Day 1 and Day 27. Overall, the systemic exposure to LE was low with a mean Cmax of 0.682 ng/mL or less.

7 Genetic Toxicology

No additional studies were needed. The genotoxicity studies for loteprednol etabonate were reviewed under NDA 20 583.

The results of the four *in vitro* genotoxicity studies (*Ames* test, Rec assay, human lymphocytes and mouse lymphoma assays) with loteprednol etabonate showed that loteprednol etabonate was not mutagenic or clastogenic. No evidence of *in vivo*, mutagenicity was observed in the mouse micronucleus test at doses up to 4000 mg/kg/bw (equivalent to an exposure of ~650,000 times the anticipated human dose).

7.4 Other Genetic Toxicity Studies

No additional studies were submitted. Other genotoxicity study(ies) for loteprednol etabonate were reviewed under NDA 20 583. This included an additional *Ames* assay using degraded loteprednol etabonate which contains a higher level of impurities than the initial drug (Study No. 06TR95-004-R1). Results of this study showed that loteprednol etabonate was not mutagenic, with or without metabolic activation, in five *Salmonella typhimurium* strains tested.

8 Carcinogenicity

Since waivers for carcinogenicity studies were granted for other loteprednol etabonate products (Lotemax®, Alrex®, and Zylet®; NDAs 20 583, 20 803, and 50 804), carcinogenicity studies were waived for this submission. This was communicated in a preNDA meeting on April 29, 2011.

9 Reproductive and Developmental Toxicology

No additional studies were needed. The reproductive toxicology studies for loteprednol etabonate were conducted under NDA 20583.

Pivotal reproductive and developmental toxicity studies with loteprednol etabonate were conducted in the rat (three studies) and rabbit (one study) using oral gavage administration. In rats, loteprednol etabonate showed maternal toxicity at all doses tested (0.5, 5.0, and 50.0 mg/kg/day) tested and toxicity in the male animals at the high dose, 50.0 mg/kg/day. Fertility and mating was unaffected but pregnancies and pregnancy outcomes were significantly affected. Based on body weight decreases and umbilical hernia findings in the mid and high dose groups, the NOAEL was 0.5 mg/kg/day.

Embryo-fetal development studies were conducted in both rats and rabbits. Rats were dosed at 0.5, 5, 50, or 100 mg/kg/day and the rabbits received lower doses of 0.1, 0.5, 3.0 mg/kg/day. In rabbits, maternal toxicity (lower body weight gain) was observed at ≥ 3 mg/kg/day group. There was clear evidence of teratogenicity in the offspring at 50 and 100 mg/kg/day (e.g. cleft palate, umbilical herniation), but not at 0.5 and 5 mg/kg/day. In the rabbit study, loteprednol etabonate did not result in embryo-fetal toxicity at up to 0.5 mg/kg/day. The NOAEL for maternal effects in the rabbit was ≤ 0.5 mg/kg/day.

10 Special Toxicology Studies

11 Integrated Summary and Safety Evaluation

The nonclinical safety profile of loteprednol etabonate (LE) has been extensively evaluated as a 0.5% ophthalmic suspension, Lotemax®, under NDA 20583 (FDA approval in March 1998). There are also two marketed products, Zylet® and Alrex®, containing LE currently on the market (loteprednol etabonate 0.5%/tobramycin 0.3%; NDAs 21675 and 50804 and loteprednol etabonate suspension 0.2%, NDA 20803 with FDA approvals in December 2004 and March 1998).

Nonclinical 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 20583. To specifically support the development and registration of the loteprednol etabonate 0.5% gel formulation, three pharmacokinetic distribution studies and two repeat dose ocular studies were conducted in rabbits. The results from the three ocular PK studies using the polycarbophil gel formulation indicate that ocular

exposure to loteprednol etabonate following topical ocular administration in a polycarbophil gel formulation is somewhat greater in the tear and conjunctiva but exposure in the cornea and aqueous humor is similar to that observed with the Lotemax suspension. The results of the toxicology studies showed no significant ocular findings during the course of the study and the ocular NOAEL to be 0.7% and the systemic NOAEL was less than 0.4%.

The formulation of 0.5% loteprednol etabonate ophthalmic gel contains 5 mg/g loteprednol etabonate as a preserved ophthalmic gel. Loteprednol etabonate is the active pharmaceutical ingredient (API) and is the same sterile form of the API that has been approved and marketed for over a decade in approved products. The inactive ingredients in the formulations are within the limits of previously approved ophthalmic drug products (CDER Inactive Ingredient Search for Approved Drug Products). Therefore, the proposed gel formulation appears acceptable.

The current label for the marketed loteprednol etabonate (LE) stated that LE was not genotoxic in a battery of genotoxicity tests. LE has been shown to be embryotoxic and teratogenic. Carcinogenicity studies were waived.

Loteprednol etabonate ophthalmic gel, 0.5% is indicated for treatment of inflammation and pain following ocular surgery. The proposed clinical dose is ocular administration of 1-2 drops into the conjunctival sac of the affected eye(s) 4x/daily after surgery and continuing throughout the first 2 weeks of the post-operative period.

The approval of NDA 202 872, 0.5% loteprednol etabonate ophthalmic gel is recommended from the pharmacology/toxicology perspective.

12 Appendix/Attachments

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/s/

ROBEENA M AZIZ
08/24/2012

LORI E KOTCH
08/24/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202872 Applicant: Bausch & Lomb Stamp Date: 11-29-11

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

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The waiver for carcinogenicity study has been granted previously.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

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

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The human dose multiples are expressed in mg/kg/day, as is acceptable for some ocular drugs.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Conrad H. Chen, Ph.D. 1-4-2012

 Reviewing Pharmacologist Date

Terry Miller, Ph.D.

 Team Leader (Acting) Date

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

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/s/

CONRAD H CHEN
01/25/2012

TERRY J MILLER
01/27/2012

Pharmacology/Toxicology Review

Pre-NDA: 202872 (for Pre-NDA meeting scheduled for April 29, 2011)

Sponsor: Bausch & Lomb, Inc., Tampa, FL 33637

Drug: Loteprednol Etabonate Ophthalmic Gel, 0.5%

Date of Submission: March 23, 2011

Submission History:

A Pre-IND 102,654 meeting was held on August 4, 2008

An EOP-2 meeting was held on August 26, 2009

IND 102,654 submitted on September 30, 2009

Date of Review completion:

April 22, 2011

Division: Division of Anti-Infective and Ophthalmology Products

Reviewer Name: Conrad H. Chen, Ph.D.

Drug Class: Corticosteroid

Generic name or Code name: Loteprednol Etabonate (LE), P-5604, OPC-5604, HGP-1, BOL-303011-X

CAS Registry Number: 82034-46-6

Chemical Name: Androsta-1, 4-diene-17-carboxylic acid, 17- [(ethoxycarbonyl)oxy]-11-hydroxy-3-Oxo, chloromethyl ester, (11 β , 17a)

Molecular Formula: C₂₄H₃₁ClO₇

Molecular Weight: MW 466.96

Related IND/NDA/BB-IND/BLA: IND 32,432 (ointment), NDA 20-583 (suspension), NDA 50-804 [REDACTED]^{(b)(4)}, and NDA 20-803 (suspension), IND 102654 (0.5% gel, submitted on September 30, 2009)

Indication: Treatment of inflammation and pain following ocular surgery

Route of Administration:

Instillation of one to two drops in the post-surgical eye four times daily for 14 days.

Formulation:

The formulation was previously called ‘0.5% LE Ophthalmic Gel Drop’ during Pre-IND stage but is called ‘0.5% LE Ophthalmic Gel’ in the current IND submission. The composition of the formulation is shown in the following tables:

Table P.1-1: Qualitative and quantitative composition of loteprednol etabonate ophthalmic gel drop, 0.5%

Component	Function	Concentration	
		mg/g*	%w/w*
Loteprednol Etabonate	Active	5.00	0.500
Edetate Disodium Dihydrate, USP			(b) (4)
Glycerin, USP			
Propylene Glycol, USP			
Boric Acid, NF			
Polycarbophil, USP			
Sodium Chloride, USP			
Purified Water, USP			
Tyloxapol, USP			
Sodium Hydroxide (b) (4)			
Benzalkonium Chloride Solution, (b) (4) USP			

* composition will be converted to industry standard weight/volume when additional density information is available
 † label claim for BAK is 30 ppm or 0.003%

The inactive ingredients in the formulations are within the limits of previously approved ophthalmic drug products (CDER Inactive Ingredient Search for Approved Drug Products).

It is noted that the drug product named 0.5% LE Ophthalmic Gel is the same product previously named as 0.4% LE Ophthalmic Suspension except for the LE content (see Memo for Pre-IND Meeting dated August 4, 2008). Another difference between the formulations is the content of preservative Benzalkonium Chloride (b) (4) vs. 0.1%.

Proposed mechanism of action:

 (b) (4)

Previous Human Experience:

There are three loteprednol etabonate containing ocular products currently on the market: Lotemax® Ophthalmic Suspension 0.5% (NDA 20-583, approved Mar. 1998), (b) (4) and Alrex® (loteprednol etabonate suspension 0.2%, NDA 20803 approved Mar. 1998) Loteprednol Etabonate Ophthalmic Gel, 0.5% (IND 102654, clinical study on-going)

Proposed Clinical Dose:

Instill 1 to 2 drops to the diseased eye(s) 4 times a day (QID) for 14 days.

Previous Nonclinical studies:

The sponsor referred to previously approved Lotemax[®], Alrex[®], and IND 32,432 for the nonclinical information. The sponsor also conducted ocular pharmacokinetic and ocular toxicology bridging studies for the current formulation of LE (i.e. polycarbophil-based gel drop) in comparison with the marketed LE products.

A list of the completed nonclinical studies conducted to support the development of LE gel is presented in Table 1 below:

Table 1: Listing of nonclinical studies conducted using LE gel

Study Type	Test System	Route of Admin.	Report No.
Pharmacology – No nonclinical pharmacology studies have been conducted with the gel formulation			
Pharmacokinetics			
Distribution	Ocular PK – LE dose vs. exposure with gel formulation, rabbit	Ocular	BL08009
	Ocular PK – Formulation comparison of gel formulation vs Lotemax, rabbit	Ocular	BL08010
Toxicology			
Repeat dose toxicity	29-day toxicity, rabbit (gel)	Ocular	6104-275
	27-day toxicity/toxicokinetics, rabbit (gel)	Ocular	6104-295

These studies have been reviewed under IND 102654 dated October 27, 2009.

Based on the human experience with marketed LE ophthalmic products and the previously conducted animal ocular toxicity studies along with bridging ocular studies with new formulation, the proposed clinical studies in the IND 102654 were allowed to proceed.

Summary of Pharmacokinetics: In general, the results showed that the polycarbophil-based formulation afforded somewhat higher ocular exposure in tear and conjunctiva, but the exposure in cornea and aqueous humor was similar to the marketed products. According to the sponsor, the systemic exposure to LE following ocular administration of the polycarbophil-based formulation was very low, consistent with that observed with the Lotemax[®] formulation. The plasma LE concentrations were < 1 ng/mL in most animals.

Summary of Toxicology: In general, the results showed that the polycarbophil-based gel drop afforded somewhat higher ocular exposure in tear and conjunctiva, but the exposure in cornea and aqueous humor was similar to the marketed products. According to the sponsor, the systemic exposure to LE following ocular administration of the polycarbophil-based gel drop was very low, consistent with that observed with the Lotemax[®] formulation. The plasma LE concentrations were < 1 ng/mL in most animals. In a 29-day repeat dose ocular toxicity study in rabbits with 7-day recovery period, there are no significant ocular findings during the course of the study and the ocular NOAEL was 0.7%. Decrease in actively growing hair follicles, evident in both the eyelids of treated animals, was observed; the eyelashes and meibomian glands were not affected. This was concluded to be related to a dermal exposure to the test article during dosing and is consistent with the known steroid modulation of their follicle cycling. Systemically, there were decreases in absolute and relative adrenal weights with a

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

The sponsor states that the purpose of the Pre-NDA meeting is to seek Agency's advice for the NDA submission.

The following nonclinical questions were addressed:

Question #1: Does the Agency agree that the nonclinical development package described in the meeting package is adequate to support the NDA submission and review for loteprednol etabonate ophthalmic gel, 0.5%?

Agency Response: Agree. (CC)

Question #2 Does the Agency agree that based on the well-established safety profile of loteprednol etabonate there is no need to conduct a carcinogenicity study and a waiver will be granted?

Agency Response: Waivers for carcinogenicity studies were granted previously for other LE products (Lotemax, Alrex, and Zylet; NDAs 20-583, 20-803, and 50-804, respectively). The waiver is also recommended for this NDA. (CC)

Signatures:

Reviewer Signature ___ Conrad H. Chen, Ph.D. _____

Team Leader Signature ___ Wendelyn Schmidt, Ph.D. _____

Concurrence Yes ___ No ___

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/s/

CONRAD H CHEN
04/25/2011

WENDELYN J SCHMIDT
04/25/2011