CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200738Orig1s000

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/BLA REVIEW AND EVALUATION

Application number:	200-738
Supporting document/s:	0000
Applicant's letter date:	12/22/2009
CDER stamp date:	12/23/2009
Date of review completion:	6/18/2010
Product:	Loteprednol Etabonate Ophthalmic Ointment, 0.5%
Indication:	Treatment of post-operative inflammation and pain following ocular surgery
Applicant:	Bausch & Lomb Incorporated
Review Division:	Division of Anti-Infective and Ophthalmology Products
Reviewer:	Conrad H. Chen, Ph.D.
Supervisor/Team Leader:	Wendelyn Schmidt, Ph.D.
Division Director:	Wiley Chambers, MD
Project Manager:	Fariba Izadi, Pharm. D.

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

The reviewer recommends the approval of NDA 200-738.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The proposed labeling is similar to that of Loteprednol Etabonate Ophthalmic Suspension 0.5% (Lotemax®). (b) (4)

Since the 70 kg is the currently accepted average human body weight, the multiples of animal dose to human dose should be recalculated accordingly.
The corrected multiples of doses (on the basis of 70 kg human body weight) are shown with underline. The calculation can be found in **Integrated Summary and Safety Evaluation** in the review. (b) (4)

8.1 Pregnancy
Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (176 ~~150~~ times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (29 ~~25~~ times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥ 5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥ 50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥ 50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (29 ~~25~~ times the maximum daily clinical dose) during organogenesis did not result in any reproductive toxicity.
Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥ 5 mg/kg/day.
Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day**.** Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.
LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate.
Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (2941

(b) (4) and 1470 (b) (4) times the maximum daily clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

(b) (4)

1.2 Brief Discussion of Nonclinical Findings

The nonclinical safety profile of loteprednol etabonate (LE) has been extensively evaluated as a 0.5% ophthalmic suspension under NDA 20-583 (approved March 1998). For the development of 0.5% loteprednol etabonate ophthalmic ointment, the sponsor has conducted 28-day ocular toxicity studies in rabbits and dogs. The study reports showed no significant toxicity findings except for the transient irregular aspect of ocular surface (in both treated and control groups) caused by the viscous consistency of the ointment vehicle.

The formulation of 0.5% loteprednol etabonate ophthalmic ointment contains (b) (4) mineral oil (USP) and (b) (4) petrolatum (USP) (b) (4). Many of the FDA approved ophthalmic drug products contain up to 59.5% mineral oil and up to 85% petrolatum. Therefore, the proposed ointment formulation appears acceptable.

2 Drug Information

2.1 Drug: Lotemax Ophthalmic Ointment 0.5%

2.1.1 CAS Registry Number (Optional)

82034-46-6

2.1.2 Generic Name: Loteprednol Etabonate Ophthalmic Ointment 0.5%

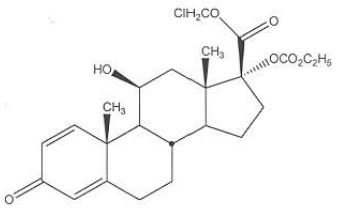
2.1.3 Code Name: LE, HGP-1, P-5604, OPC-5604, BOL-303011-X

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

2.1.5 Molecular Formula/Molecular Weight:

$C_{24}H_{31}ClO_7$/466.96

2.1.6 Structure



2.1.7 Pharmacologic class: Corticosteroid

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 20-583, Lotemax® Ophthalmic Suspension 0.5% (loteprednol etabonate 0.5%), approved March 1998.
NDA 50-804 (NDA 21-675), Zylet (loteprednol etabonate 0.5%/tobramycin 0.3%), approved Dec. 2004.
NDA 20-803, Alrex® (loteprednol etabonate 0.2%), approved March 1998.
(b) (4)
IND 32,432 Lotemax Ophthalmic Ointment 0.5%

2.3 Clinical Formulation

2.3.1 Drug Formulation:

Table P.1-1: Qualitative and Quantitative Composition of Loteprednol Etabonate Ophthalmic Ointment, 0.5%

Component	Function	Concentration	
		(mg/g)	%w/w
Sterile Loteprednol Etabonate	Active	5.0	0.5
Mineral Oil, USP	(b) (4)		
White Petrolatum, USP			

2.3.2 Comments on Novel Excipients

The formulation of 0.5% loteprednol etabonate ophthalmic ointment contains (b) (4) mineral oil (USP) and (b) (4) petrolatum (USP) as the (b) (4) Many of the FDA approved ophthalmic drug products contain up to 59.5% mineral oil and up to 85% petrolatum. Therefore, the proposed ointment formulation appears acceptable.

2.3.3 Comments on Impurities/Degradants of Concern

The degradation products for loteprednol etabonate in the drug product are (b) (4) are considered the primary impurities/degradation products in the LE-based drug products. (b) (4) The acceptance criteria for these degradants will be discussed in the chemist review.

(b) (4) is a leachable originating from the (b) (4) An acceptance criterion of NMT (b) (4) is used by the sponsor for both release testing and shelf life. The chemistry reviewer has requested the pharm/tox input for the safety of (b) (4) in the drug product.
The sponsor has calculated the potential daily exposure at (b) (4) as follows:
30 mg (1/2 inch ribbon) ointment x 8 doses = 240 mg ointment/day
240 mg ointment/day x (b) (4) = (b) (4)
The sponsor cited the Maximum Allowable Dose Level, under California legislation (Office of Environmental Health Hazard Assessment (OEHHA) for Reproductive and Cancer Hazard Assessment Section, June 2007, for (b) (4)
Although we are unfamiliar with the standard set by the OEHHA, I think the calculation made by the sponsor is sensible.
According to the literature, (b) (4) is relatively nontoxic. The LD50s for rodents are in the 8 to 10 g/kg range. Rats that were given 1 mg/kg of a solution in oil twice weekly for six weeks developed no abnormalities. Growth inhibition was seen in one group of rats who were given (b) (4) in their diet for one year.
Splash contact has caused immediate, severe, stinging pain which stimulated profuse tearing. This tearing generally washes the liquid away and prevents the eyes from being damaged. No other information regarding topical ocular toxicity of (b) (4) could be found.
It is therefore concluded that the proposed acceptance criterion of (b) (4) (b) (4) seems acceptable.

2.4 Proposed Clinical Population and Dosing Regimen

LOTEMAX ointment is indicated for the treatment of post-operative inflammation and pain following ocular surgery.
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.
The ½ inch ribbon has a mass of 30 mg of ointment. Therefore, the amount of

0.5% loteprednol etabonate (LE) in each dose is:
30 mg ointment/dose x 0.005 mg LE/mg of ointment = 0.15 mg LE/dose
The daily clinical dose to both eyes in humans is calculated as:
0.15 mg LE/dose x 8 doses/day÷50 kg body weight = 0.024 mg LE/kg/day
0.15 mg LE/dose x 8 doses/day÷60 kg body weight = 0.02 mg LE/kg/day
0.15 mg LE/dose x 8 doses/day÷70 kg body weight = 0.017 mg LE/kg/day

2.5 Regulatory Background

Lotemax® Ophthalmic Ointment 0.5% was studied under IND 32432.

3 Studies Submitted

3.1 Studies Reviewed

1. Pharmacokinetics of loteprednol etabonate and its metabolites following a single topical ocular administration of loteprednol etabonate suspension and ointment formulations in pigmented rabbits with ocular inflammation
2. Loteprednol etabonate ointment, 0.5%; 28 day ocular tolerance study in albino rabbits receiving four times per day instillation
3. 4-week ocular tolerance study following 4 times daily administration in beagle dogs

3.2 Studies Not Reviewed

The GLP-compliant toxicology package for loteprednol etabonate was submitted previously as part of NDA 20-583 and/or NDA 50-804 (Zylet). Those studies will not be reviewed here.

3.3 Previous Reviews Referenced

NDA 20-583 (Lotemax® Ophthalmic Suspension 0.5%) and NDA 50-804 (Zylet, loteprednol etabonate 0.5%/tobramycin 0.3%)

4 Pharmacology

Referred to NDA 20-583

Primary Pharmacology

Results from competitive binding studies indicate that LE has a binding affinity for glucocorticoid (Type II) receptors that is 4.3-times greater than that of transcortin. In contrast, the LE metabolites, PJ-90 and PJ-91, did not bind to the glucocorticoid receptor.
The primary anti-inflammatory activity of LE has been demonstrated in several *in vivo* systems. Studies in three models of anterior ocular inflammation (*i.e.*, paracentesis

induced breakdown of the blood-aqueous-barrier, acute and chronic uveitis, and corneal inflammation) were conducted to evaluate LE when administered topically to the eye. Efficacy was observed in these studies. The *in vivo* anti-inflammatory activity of LE was also studied in multiple non-ocular models of inflammation (croton oil-induced ear edema, DNFB-induced dermatitis, cotton pellet-induced granuloma, histamine-induced vascular permeability, carrageenan-induced skin and paw edema, and adjuvant-induced arthritis) in mice and rats.

4.2 Secondary Pharmacology

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

The safety pharmacology battery is not available for LE.

5 Pharmacokinetics/ADME/Toxicokinetics

Referred to NDA 20-583.

5.1 PK/ADME

Multiple studies were conducted as part of the development of the LE suspension products, Lotemax® and Alrex®, to assess the ocular and systemic pharmacokinetics of LE, along with the metabolism and excretion of LE and its metabolites. Data for these legacy studies were submitted as part of NDA 20-583 (Lotemax). A new study is submitted as follows:

Pharmacokinetics of loteprednol etabonate and its metabolites following a single topical ocular administration of loteprednol etabonate suspension and ointment formulations in pigmented rabbits with ocular inflammation:

Key study findings: Results from the present study show that administration of LE in an ointment formulation afforded similar ocular and systemic exposure compared with the same dose in a suspension formulation.
Study Number: BL05020

Test Facility (b) (4)
Final report date: June 11, 2007
Method: A total of 132 Fauve de Bourgogne (pigmented) rabbits were used in this non-GLP, non-crossover study. The in-life portion of the study was conducted at (b) (4); bioanalysis was conducted at (b) (4). The test formulations were prepared by Bausch & Lomb formulations department and shipped and stored at room temperature until use. Ocular inflammation was induced in the animals 24-hr prior to the start of the study with a single (30 µL) intrastromal injection of clove oil into the cornea of the right eye. The test formulations were administered to separate groups of animals as a single topical instillation (50 µL) to the inflamed right eye. Subgroups of 6 rabbits were euthanized at predetermined time points following dose administration (5, 15, 30, 60, and 90 min and 2, 4, 6, 8, 12 and 24 hr) and the right eye was enucleated and dissected. Blood and ocular tissue (conjunctiva, cornea, and aqueous humor) samples were collected from each animal and stored at -20◦ C until analysis. The concentration of LE, PJ-90 and PJ-91 in plasma and ocular tissue samples was determined using a reversed-phase liquid chromatography system coupled to a tandem mass spectrometer (LC/MS/MS). Pharmacokinetic analysis of the concentration vs. time data for each analyte and tissue was performed using non-compartmental methods (WinNonlin version 4.1, Pharsight Corp., Cary, NC).
Results: A summary of the pharmacokinetic parameters is shown in the following table.

Table 1 Summary of PK Parameters for LE, PJ-90 and PJ-91 in Plasma and Ocular Tissues Following Single Topical Ocular Administration to Rabbits with Inflamed Eyes

Tissue	Formulation	Analyte	Cmax[a] (ng/g)	Tmax (min)	AUC(0-t) (min•ug/g)
Aqueous Humor	Suspension	LE	29.3	30	5.03
		PJ-91	54.1	15	3.77
		PJ-90	19.9	15	1.13
	Ointment	LE	72.4	5	9.82
		PJ-91	2.67	90	0.511
		PJ-90	NC[b]	NC	NC
Conjunctiva	Suspension	LE	3624	90	366
		PJ-91	46.6	5	1.61
		PJ-90	6.34	5	0.240
	Ointment	LE	2060	15	347
		PJ-91	15.9	15	0.689
		PJ-90	NC	NC	NC
Cornea	Suspension	LE	1403	60	198
		PJ-91	457	5	23.8
		PJ-90	92.5	5	4.55
	Ointment	LE	1161	30	282
		PJ-91	71.5	5	6.87
		PJ-90	14.4	5	0.643
Plasma	Suspension	LE	0.354	15	0.0480
		PJ-91	NC	NC	NC
		PJ-90	NC	NC	NC
	Ointment	LE	0.103	60	0.0360
		PJ-91	NC	NC	NC
		PJ-90	NC	NC	NC

[a] For Cmax, the mean (N=5) ± SD from each animal at Tmax is presented
[b] NC – Not calculated, too few measurable values to derive useful PK estimates.

In the present study, topical administration of LE in either an ointment or a suspension formulation provided similar ocular exposure to LE in rabbits with corneal inflammation. From the tissues collected, LE concentrations were observed to be highest in conjunctiva followed by cornea, aqueous humor and plasma after the administration of the suspension or the ointment formulation. Also, exposure to LE from the ointment or the suspension formulation in different ocular tissues was observed to be greater than that of either PJ-90 or PJ-91. Further, systemic exposure to LE following topical administration of the ointment or the suspension formulation was found to be minimal.

5.2 Toxicokinetics

The details of toxicokinetics are described in the repeat dose ocular toxicity studies in rabbits and dogs.
The pharmacokinetic properties of LE, formulated in a novel ointment formulation, have been investigated *in vivo* following a single topical ocular administration to rabbits with corneal inflammation. Results from this study indicated that topical ocular instillation of LE in the ointment formulation afforded similar ocular and systemic exposure to LE and its metabolites compared with the currently marketed Lotemax suspension formulation in rabbits (See 5.1 above).

6 General Toxicology

Summary of Systemic Toxicity: The systemic toxicity of LE was previously assessed following single and repeat dosing via oral and subcutaneous (SC) administration routes. These studies were previously submitted and reviewed under NDAs 20-583 and 50-804.
Evaluations of systemic effects were also conducted in the chronic ocular dosing studies with LE in a suspension formulation conducted in rabbits (NZW) for 26 weeks and dogs (Beagle) for 52 weeks and LE in combination with tobramycin, 0.3% in Dutch-Belted rabbits for 26 weeks. No significant organ-related toxicity was observed following ocular administration of LE to rabbits (0.5% LE, QID) for 26 weeks or to dogs (0.05 [once daily], 0.1 and 0.5% LE [BID]) for 52 weeks. In the 52-week dog study, a parallel group was treated with dexamethasone (BID). This latter group demonstrated systemic changes typical of corticosteroids (changes in liver, adrenal glands, thymus), whereas these changes were not observed in the LE-treated groups. In the 26-week study in rabbits, the rabbits were treated with topical ocular doses of LE, 0.5% alone or in combination with tobramycin, 0.3% (LET) six times per day; a group of rabbits was also treated with LET four times per day. In the LE and LET six times per day groups, a higher incidence of effects on the adrenal glands (small and/or flabby, low weight, atrophy of the zona fasciculata, and/or increased pigmentation) was observed. A few animals in the four times per day group also had adrenal changes. **The subject of this NDA, 0.5% LE ointment, did not demonstrate ocular or systemic toxicity effects when evaluated in two 28-day ocular tolerance studies.**
The potential toxicity was also evaluated for a metabolite of LE, PJ-90 by both an acute subcutaneous dosing study in rats (10, 30, and 100 mg/kg) and acute and repeat topical ocular dosing in rabbits (0.5% PJ-90). No adverse systemic effects were noted in any of these studies.

6.1 Single-Dose Ocular Toxicity

No new data. Referred to NDA 20-583

6.2 Repeat-Dose Ocular Toxicity

Study title: Loteprednol etabonate ointment, 0.5%; 28 day ocular tolerance

study in albino rabbits receiving four times per day instillation

Study no.:	B16F0805
Study report location:	Not stated
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 17, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AAP021

Key Study Findings

LE, 0.5% ointment was well-tolerated when administered topically to the eyes of NZW rabbits QID for 28 days. No adverse systemic effects were observed.

Methods

Doses:	Animals were treated with LE ointment or vehicle, 50 µL in the right eye
Frequency of dosing:	QID for 28 consecutive days
Route of administration:	Topically onto the right eye with micropipette
Dose volume:	50 µL
Formulation/Vehicle:	0.5% LE ointment and ointment vehicle
Species/Strain:	New Zealand White rabbit
Number/Sex/Group:	5/sex/group
Age:	4 weeks of age
Weight:	2135-2558 gm
Satellite groups:	None
Unique study design:	Blood samples were collected at 1, 2, 3 and 24 hours after the first daily instillation on Day 1 and one day of fourth week, in order to determine LE, PJ90 and PJ91 concentration in plasma.

Observations and Results

There were no unscheduled deaths during the course of the study. The bioanalyses of the plasma levels of LE, PJ-91 and PJ-90 were not considered to be valid as the QC values were out of the acceptable range (85 – 115%) and the absence of plasma stability data at the date that the samples were analyzed. There were no ophthalmic findings that suggested an adverse effect due to LE, 0.5% ointment. Some transient mild signs of irritation (redness and chemosis) were observed during the study, as well as retained fluorescein on the surface of the eye. As these were found in both treated and control eyes, the findings were not considered toxicologically relevant. There were no changes, either in clinical evaluations or post-mortem examinations, indicating a systemic effect.

Toxicokinetics

The sponsor states that the data for concentrations of LE, PJ90 and PJ91 in plasma will be reported in an amendment. However, the submission also states that "the obtained toxicokinetic results were not considered to be valid". No conclusion regarding the toxicokinetic findings of the study was given. The sponsor was contacted on May 24 and June 2, 2010 for clarification of this issue.
On June 10, 2010, the sponsor provided an explanation stating that the toxicokinetics data in the 28-day rabbit ocular toxicity study were not valid because of QC issues. However, the sponsor described that loteprednol etabonate and its metabolites were below the lower limit of quantitation (4 ng/mL) in most samples in the study.
Sponsor referred to Study BL05020 to indicate that the systemic exposure to loteprednol etabonate and its metabolites following topical ocular administration of the loteprednol etabonate ophthalmic ointment 0.5%, was no higher than the systemic exposure observed following topical ocular administration of the loteprednol etabonate ophthalmic suspension, 0.5% (Lotemax®). This reviewer has decided to accept the sponsor's explanation of the study. No further action will be necessary.

Study title: 4-week ocular tolerance study following 4 times daily administration in beagle dogs

Study no.:	AA28056
Study report location:	Not stated
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AAP-021

Key Study Findings

LE, 0.5% ointment was well-tolerated when administered topically to the eyes of Beagle dogs QID for 28 days. No adverse systemic effects were observed.

Methods

Doses:	
Frequency of dosing:	QID for 28 days
Route of administration:	Topical ocular
Dose volume:	The left eye of each animal was dosed QID with one band (0.154 g – 0.778 g/group/dose) per dose of the ointment formulation.
Formulation/Vehicle:	0.5% LE ointment or ointment vehicle
Species/Strain:	Beagle dogs
Number/Sex/Group:	3/sex/group
Age:	5 months of age
Weight:	Males: 8 to 10 kg; Females: 9 to 10 kg
Satellite groups:	None
Unique study design:	Blood was collected once pretest and during week 4 at termination

Observations and Results

The test item, 0.5% loteprednol etabonate ointment, administered topically in the inferior conjunctival sac of the left eye of Beagle dogs, 4 times daily, for 4 weeks, did not produce any local or systemic toxicity.
There were no unscheduled deaths that occurred during the course of the study. Plasma concentrations of LE, PJ-91, and PJ-90 were below the limit of quantitation (4 ng/mL) in all samples. There were no ophthalmic findings that suggested an adverse effect due to LE, 0.5% ointment. The only finding noted was retention of fluorescein on the surface of the eye. This was not considered toxicologically relevant as it was observed in both treated and control eyes, and most likely represented the persistence of the ointment base on the surface of the eye. There were no changes, either in clinical evaluations or post-mortem examinations indicative of a systemic effect.

Toxicokinetics

All the plasma concentrations of loteprednol etabonate and its derivatives PJ90 and PJ91 were below the limit of quantitation (i.e. 4 ng/mL). Since all the plasma concentrations were below the limit of quantification, it was concluded that the test item did not pass into the systemic circulation. Consequently, no toxicokinetic evaluation was performed.

7 Genetic Toxicology

No new data. Referred to NDA 20-583.

8 Carcinogenicity

No carcinogenicity studies have been conducted.

9 Reproductive and Developmental Toxicology

No new data. Referred to NDA 20-853.

10 Special Toxicology Studies

None submitted.

11 Integrated Summary and Safety Evaluation

The nonclinical safety profile of loteprednol etabonate (LE) has been extensively evaluated as a 0.5% ophthalmic suspension under NDA 20-583 (approved March 1998). There are also two marketed products of LE currently on the market. Zylet (loteprednol etabonate 0.5%/tobramycin 0.3%, NDA 50-804 and NDA 21-675) was approved in December 2004 and Alrex (loteprednol etabonate suspension 0.2%, NDA 20-803) was approved in 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 20-583. For the development of 0.5% loteprednol etabonate ophthalmic ointment, the sponsor has conducted 28-day ocular toxicity studies in rabbits and dogs. The study reports showed no significant toxicity findings except for the irregular aspect of ocular surface caused by the viscous consistency of the ointment vehicle.

The formulation of 0.5% loteprednol etabonate ophthalmic ointment contains (b) (4) mineral oil (USP) and (b) (4) petrolatum (USP) as the (b) (4). Many of the FDA approved ophthalmic drug products contain up to 59.5% mineral oil and up to 85% petrolatum. Therefore, the proposed ointment 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. No carcinogenic studies have been conducted for LE.

LOTEMAX ointment is indicated for the treatment of post-operative inflammation and pain following ocular surgery. The proposed clinical dose is ocular administration of approximately ½ inch ribbon of 0.5% loteprednol etabonate ophthalmic ointment 4 times a day for 14 days. The ½ inch ribbon has a mass of 30 mg of ointment. Therefore, the amount of 0.5% loteprednol etabonate (LE) in each dose is 30 mg ointment/dose x 0.005 mg LE/mg of ointment = 0.15 mg LE/dose.
The daily clinical dose to both eyes in humans is calculated as:

0.15 mg LE/dose x 8 doses/day÷50 kg body weight = 0.024 mg LE/kg/day
0.15 mg LE/dose x 8 doses/day÷60 kg body weight = 0.02 mg LE/kg/day
0.15 mg LE/dose x 8 doses/day÷70 kg body weight = 0.017 mg LE/kg/day

3 mg/kg/day ÷ 0.017 mg/kg/day = 176 times
0.5 mg/kg/day ÷ 0.017 mg/kg/day = 29 times
50 mg/kg/day ÷ 0.017 mg/kg/day = 2941 times
25 mg/kg/day ÷ 0.017 mg/kg/day = 1470 times

The approval of NDA 200-738, 0.5% Lotemax ointment, is recommended from the pharmacology/toxicology perspective.

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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/s/

CONRAD H CHEN
07/16/2010

WENDELYN J SCHMIDT
07/19/2010

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 200738 **Applicant: Bausch & Lomb** **Stamp Date: 12-23-2009**
Drug Name: Lotemax®
(loteprednol etabonate ophthalmic ointment 0.5%)

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [X] No [ ]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin?	X		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	X		
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	X		The formulation to be marketed is used in the 28-day GLP repeat-dose toxicity studies in dogs and rabbits.
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		As in other ocular drug products, the human dose and animal dose were expressed in mg/kg/day basis.
7	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	X		
8	On its face, 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 sponsor submitted a rationale to justify the alternative route?	X		
9	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
10	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	X		
11	From a pharmacology perspective, is this NDA fileable?	X		

Note:

The dosing regimen of 0.5% Lotemax Ointment is described as “apply approximately ½ inch ribbon into the conjunctival sac(s) four times daily for 14 days”. However, the exact amount of loteprednol etabonate in the ½ inch ribbon of ointment is not described. This information is needed for calculating the multiples of animal dose to human dose (in mg/kg/day) in the label.
The sponsor should show the calculation how the figures in the proposed label were derived.

Reviewing Pharmacologist:

Conrad Chen, Ph.D. Date: 1-26-2010

Team Leader:

Wendelyn Schmidt, Ph.D. Date: 1-26-2010

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

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

/s/

CONRAD H CHEN
01/26/2010

WENDELYN J SCHMIDT
01/28/2010