CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200738Orig1s000

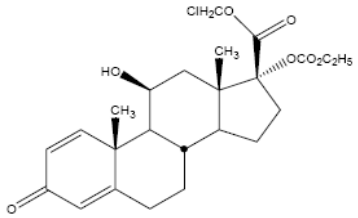
SUMMARY REVIEW

Division Director Review for NDA 200738

Date	April 13, 2011
From	Wiley A. Chambers, M.D.
NDA #	200738
Applicant	Bausch & Lomb Incorporated
Date of Submission	January 25, 2011
Type of Application	505(b)(1)
Name	Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%
Dosage forms / Strength	Topical ophthalmic ointment
Proposed Indication(s)	Treatment of post-operative inflammation and pain following ocular surgery
Action:	Approval

1. Introduction/Background

Loteprednol etabonate ophthalmic ointment (LE) is a sterile, topical, anti-inflammatory corticosteroid formulation. The drug product, developed by Bausch & Lomb (B&L), is an ophthalmic ointment containing 0.5% loteprednol etabonate. The drug is (b) (4) of white petrolatum and mineral oil.



Loteprednol etabonate has been marketed in the United States by Bausch & Lomb since 1998 as Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% and Alrex (loteprednol etabonate ophthalmic suspension) 0.2% and marketed since 2005 in a fixed combination with tobramycin as Zylet (loteprednol etabonate and tobramycin ophthalmic suspension). The product development for loteprednol etabonate ophthalmic ointment, 0.5% was conducted under IND 32,432.

Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

2. CMC

The drug substance, loteprednol etabonate, is a white to off-white powder. It is insoluble in water. The chemical name is chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate. The molecular formula is $C_{24}H_{31}ClO_7$ and the molecular weight of loteprednol etabonate is 466.96. Loteprednol etabonate is the same drug substance as is currently used in Lotemax (loteprednol etabonate ophthalmic suspension 0.5%) (NDA 20-583). The drug substance is manufactured and (b) (4). DMF (b) (4) is referenced for drug

substance information. The drug product, Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%, (b) (4)

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

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

Commercial drug product will be packaged as a nominal 3.5g fill in 3.5g tin tubes with pink LDPE caps. In addition, a physician's sample size configuration consisting of a nominal 1g fill in 2g tin tubes with pink LDPE caps is also proposed. The average weight of one dose (a ½ inch ribbon) of ointment was determined to be 30.0 mg with a standard deviation of 6.6 mg. Individual ½ inch ribbons ranged in weight from 16.2 mg to 48.7 mg.

FACILITY INSPECTIONS

The cGMP issues identified in the review of the original submission have been resolved. A re-inspection of the (b) (4) facility was completed and no deviations from cGMPs were identified. All facilities are now believed to be in compliance with cGMPs.

Drug Product Specifications:

Test	Analytical Procedure	Acceptance Criteria	
		Release	Shelf life
Description	Visual (PS-1008)	Off-white to yellowish homogeneous ointment	
Particulate Matter	Visual (PS-1013)	Essentially free of foreign particulate matter	Not applicable
Metal Particles	USP<751> (PS-1001)	(b) (4)	Not applicable
Particle Size Distribution	C-1812	(b) (4)	Not applicable
Identification A	C-1689 (HPLC)	The retention time for loteprednol etabonate peak in the sample corresponds to that of the standard	Not applicable
Identification B	C-1689 (UV)	The UV spectrum of the assay preparation exhibits its maximum at the same wavelength as that of the standard	Not applicable

Assay	C-1689 (HPLC)	95.0 – 105.0% of label claim		90.0 – 110.0% of label claim
Related Substances^	C-1689 (HPLC)	(b) (4)		
		Total Chromatographic Related Substances	NMT (b) (4)	NMT (b) (4)
(b) (4)	C-1798 (HPLC)	NMT (b) (4)		
Dose Uniformity	C-1689 (HPLC)	90-110% of Label Claim		
Leak Test	USP<771> (PS-1006)	Meets USP requirements		Not applicable
Minimum Fill	USP<755> (PS-1003)	Meets USP requirements		Not applicable
(b) (4)	C-1204 (b) (4)	NMT (b) (4)		
Sterility	USP <71> 24-T012 or B-1044	Meets USP requirements		
Endotoxin	Complies with USP <85> (72-156 or STP0046)	NMT (b) (4)		Not applicable

^ Any loteprednol etabonate synthetic process impurities, which are not also shown to be degradation products, would be controlled in the drug substance in accordance with ICH Q6A.

Note, phase 2 testing will only be performed in the event that phase 1 criteria are not met.

The proposed acceptance criterion has been revised and is now acceptable.

3. Nonclinical Pharmacology/Toxicology

The nonclinical safety profile of loteprednol etabonate (LE) has been evaluated as a 0.5% ophthalmic suspension under NDA 20-583 (approved March 1998). 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 current label for the marketed loteprednol etabonate (LE) states that LE was not genotoxic in a battery of genotoxicity tests. LE has been shown to be embryotoxic and teratogenic. No carcinogenic studies have been conducted for LE.

4. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacokinetic studies were conducted during the development of Lotemax suspension and Zylet, and these data have been submitted previously with the corresponding NDAs for these products (NDA #20-583 and #50-804, respectively). No new clinical pharmacology data was presented in this application. The pharmacokinetic data previously submitted addresses requirement for bioavailability outlined in 21 CFR 320.21.

5. Sterility Assurance

(b) (4)

The drug product is a sterile topical ophthalmic ointment in a multi-dose tube. A microbial ingress test was used to validate container closure integrity for the tin tubes. The study was performed using 3.5 g tubes with LDPE caps. Media-filled tubes were immersed in a suspension of *B. cepacia* (6.2×10^8 CFU/mL) for 20 minutes at room temperature. Following immersion, the test samples were subjected to 5 psi (above atmospheric) of pressure for 5 minutes followed by 5 minutes at 5 inches of mercury (vacuum). The test units were then incubated at 32.5±2.5°C for 7 days. After incubation, the contents of the test units were examined for evidence of microbial growth. None of the test units or negative controls (not immersed in the microbial suspension) was positive for growth. The growth promotion units (inoculated with 10-100 CFU of *B. cepacia*) and the positive control units (breached units) were positive for microbial growth.

(b) (4)

. The drug product was tested using USP <51> antimicrobial effectiveness testing. In addition to the 5 test organisms listed in USP <51>, four additional organisms were used in the test. The acceptance criteria were achieved for a USP Category 1 product (includes ophthalmic products).

6. Safety

Two clinical studies (Studies 525 and 526) were used to evaluate safety in addition to the previous studies with loteprednol suspension. There were 405 patients in the safety database who received loteprednol etabonate ophthalmic ointment. In a pooled analysis of Studies 525 and 526, the most common ocular adverse events reported with loteprednol ointment 0.5% were anterior chamber inflammation, photophobia, corneal edema, conjunctival hyperemia, eye pain, and iritis.

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%, dosed four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period, is safe for treatment of post-operative inflammation and pain following ocular surgery

Clinical/Statistical - Efficacy

Study 525: Inflammation Cleared Analysis (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Day 3	10 (5%)	9 (5%)	0.8315
Day 8 – primary endpoint	48 (24%)	27 (14%)	0.0022
Day 15	84 (42%)	30 (15%)	<0.0001
Day 18	86 (43%)	39 (20%)	<0.0001

Study 526: Inflammation Cleared Analysis (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Day 3	10 (5%)	9 (5%)	0.8020
Day 8 – primary endpoint	64 (31%)	23 (11%)	0.0001
Day 15	107 (53%)	42 (21%)	<0.0001
Day 18	100 (49%)	46 (23%)	<0.0001

Study 525: Mean ACR Count (ITT Population)

	Number of Subjects in LE Ointment	LE Ointment	Number of Subjects in Vehicle	Vehicle
Visit 1-Screening	201	0	199	0
Visit 3-POD#1 (sd)	201	3.7 (0.8)	199	3.8 (0.9)
Visit 4-POD #3 (sd)	200	2.7 (1.2)	196	3.3 (1.5)
Visit 5-POD #8 (sd)	199	1.6 (1.3)	195	3.0 (1.8)
Visit 6-POD #15 (sd)	199	1.1 (1.3)	195	2.8 (1.9)
Visit 7-POD #18 (sd)	200	1.2 (1.4)	195	2.7 (1.9)

Study 526: Mean ACR Count (ITT Population)

	Number of Subjects in LE Ointment	LE Ointment	Number of Subjects in Vehicle	Vehicle
Visit 1-Screening	203	0	202	0
Visit 3-POD#1 (sd)	203	3.7 (0.7)	202	3.7 (0.7)
Visit 4-POD #3 (sd)	202	2.5 (1.2)	202	3.1 (1.5)
Visit 5-POD #8 (sd)	201	1.5 (1.5)	201	2.9 (1.8)
Visit 6-POD #15 (sd)	200	1.0 (1.5)	201	2.6 (2.0)
Visit 7-POD #18 (sd)	201	1.1 (1.5)	199	2.6 (2.0)

Study 525: Pain Free Analysis (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Day 3	148 (74%)	85 (43%)	<0.0001
Day 8	156 (78%)	90 (45%)	<0.0001
Day 15	152 (76%)	79 (40%)	<0.0001
Day 18	125 (62%)	64 (32%)	<0.0001

Study 526: Pain Free Analysis (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Day 3	153 (75%)	95 (47%)	<0.0001
Day 8	149 (73%)	83 (41%)	<0.0001
Day 15	157 (77%)	74 (37%)	<0.0001
Day 18	132 (65%)	63 (31%)	<0.0001

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

7. Advisory Committee Meeting

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

8. Pediatrics

Bausch & Lomb requested a pediatric waiver for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% on April 30, 2010. Safety and effectiveness in pediatric patients have not been established. Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% should not be used in children following ocular surgery. Its use may interfere with amblyopia treatment by hindering the child's ability to see out of the operated eye.

9. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on September 13, 2010. Two domestic clinical sites were inspected in support of this application, Kenneth Sall, M.D. and Arthur M. Fishman, M.D.

The inspection of Dr. Sall's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, for: Failure to conduct the study according to the signed investigator statement and the investigational plan

[21 CFR 312.60]. Specifically, three employees performed duties not delegated to them (screening visits, post surgery visit, visual acuity and refraction evaluations).

Although regulatory violations were noted as above, it is unlikely based on the nature of the violations that they significantly affect the reliability of safety and efficacy data. Based on the provided EIR for this site and Dr. Sall's responses regarding the regulatory violations during the inspection, which were documented in the EIR, data derived from Dr. Sall's site are considered reliable.

The inspection of Dr. Fishman's site did not reveal regulatory violations. Based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Fishman's site are considered acceptable.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated "Lotemax" as the proposed proprietary name for loteprednol etabonate ophthalmic ointment. DMEPA approved proprietary name in a letter dated June, 4, 2010.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%. DDMAC provided recommendations on the packaging configuration and the package insert labeling in a separate review and in a labeling meeting held on September 13, 2010.

10. Labeling

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% labeling was submitted on April 13, 2011. The labeling has been reviewed and is considered acceptable.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

11. Regulatory Action

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

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

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

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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

/s/

WILEY A CHAMBERS
04/14/2011