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APPLICATION NUMBER:
200738Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 200738

Date	April 12, 2011
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	200738
Applicant	Bausch & Lomb Incorporated
Date of Submission	January 21, 2011
PDUFA Goal Date	January 21, 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
Recommended:	Recommended for Approval

1. Introduction

Loteprednol etabonate ophthalmic ointment (LE) is a sterile, topical, anti-inflammatory corticosteroid formulation. The drug product, developed by 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).

NDA 200738 received a Complete Response letter on October 20, 2010. With the resolution of all remaining Chemistry and Manufacturing issues and inspections, the application for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is now recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery.

The product development for loteprednol etabonate ophthalmic ointment, 0.5% was conducted under IND 32,432.

2. Background

NDA 200738 received a Complete Response Letter dated 10/20/10. The letter cited two deficiencies:

- 1) Manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. Please amend the application with facilities that are in

compliance with current good manufacturing practice (cGMP) or notify us when all currently submitted facilities are in compliance with cGMPs.

2) The proposed controls for the drug product are inadequate to preserve the quality or stability of the drug product. Specifically, the wide acceptance criteria do not provide adequate control on dose uniformity. The acceptance criteria should be based on data from homogeneous samples at release with a narrower range than currently proposed. The dose uniformity test with appropriate acceptance criteria should be able to identify settling in samples during stability. When responding to this deficiency, please submit the complete data set from the stability studies.

3. CMC

Revised labeling and the remaining Chemistry and Manufacturing issues cited in the October 20, 2010, Complete Response letter have been addressed by the applicant in an amendment dated January 21, 2011. For detailed information regarding each of the deficiencies, see the CMC reviews dated April 8, 2011, and April 12, 2011.

There is a typographical error in the April 12, 2011, CMC review. On page 8, the sentence, “*An “Acceptable” site recommendation from the Office of Compliance has not been made on April 12, 2011 (See Attachment).*” should read, “*An “Acceptable” site recommendation from the Office of Compliance has been made on April 12, 2011 (See Attachment).*”

Per the CMC reviews dated April 8, 2011, and April 12, 2011:

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

An “Acceptable” site recommendation from the Office of Compliance has been made.

Therefore, from the CMC perspective, this NDA is recommended for approval.

The applicant provided a revised method and updated acceptance criteria of 90-110% of label claim for the content uniformity test in the Drug Product Specification. The analytical procedure “Assay and Related Substances by HPLC (C-1689)” was adequately modified to include content uniformity testing. Method validation was updated. Content uniformity results at release and for aged samples support the adequacy of the proposed acceptance criteria of 90-110% of label claim.

Drug Product Specification (Updated Jan 24, 2011)

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)
(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.

4. Nonclinical Pharmacology/Toxicology

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 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.

5. 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.

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 7/2/2010:

(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 $32.5 \pm 2.5^\circ\text{C}$ 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).

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 9/27/2010:

Analyses of Primary Endpoints

The hierarchical primary efficacy endpoints for these two phase 3 studies were:

1. The proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (POD# 8)
2. The proportion of subjects with Grade 0 (no pain) at Visit 5 (POD# 8).

Two clinical studies (Studies 525 and 526) were used to evaluate efficacy. These studies were randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies to evaluate the clinical safety and efficacy of LE ophthalmic ointment, 0.5% compared to vehicle for the treatment of inflammation following cataract 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 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.

8. Safety

From the original Medical Officer Review dated 9/27/2010:

Two clinical studies (Studies 525 and 526) were used to evaluate safety. Between the 2 studies there were 405 patients in the safety database who received loteprednol etabonate ophthalmic ointment.

Only one dosing regimen was studied, Lotemax ointment 0.5% QID.

Long-term safety and effectiveness were not evaluated for the clinical studies. The duration of treatment for the subjects in these trials was no longer than 14 days. Loteprednol etabonate ophthalmic ointment is intended for short-term use for the treatment of inflammation and pain following ocular surgery.

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.

Corticosteroids have a known risk of increasing IOP, and therefore IOP was monitored at every visit. There were no deaths in either Study 525 or 526.

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

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.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. 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.

11. Other Relevant Regulatory Issues

With the resolution of all remaining Chemistry and Manufacturing issues and inspections, the application for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is now recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery.

12. Labeling

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery based on the outstanding cGMP issues.

Labeling revisions have been recommended by the review team and have been incorporated into the recommended labeling.

See Appendix 1 for the recommended labeling for the drug product.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery.

RISK BENEFIT ASSESSMENT:

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.

When looking at the Intent-to-Treat (ITT) population for complete resolution of AC cell/flare and pain, loteprednol etabonate ophthalmic ointment, 0.5% is superior to vehicle in Studies 525 and 526. The results of the Per-Protocol PP analysis are similar to the ITT analysis.

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.

The benefits of using this drug product outweigh the risks for the above indication.

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

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

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

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

/s/

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04/14/2011

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04/14/2011