

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202872Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: August 16, 2012

To: June Germain, Regulatory Project Manager
Division of Transplant and Ophthalmology Products

William Boyd, MD, Medical Officer
Division of Transplant and Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: NDA 202872
loteprednol etabonate ophthalmic gel 0.5%

As requested in your consult dated January 24, 2012, DPDP has reviewed the draft labeling for TRADENAME™ (loteprednol etabonate ophthalmic gel) 0.5%. We acknowledge that a trade name has not yet been approved for this NDA.

DPDP's comments are based on the substantially complete version of the labeling titled, "NDA 202872 draft PI 8-7-12.doc," which was sent via email from June Germain on August 7, 2012.

DPDP's comments are provided in the attached, clean version of the labeling.

If you have any questions about DPDP's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.corser@fda.hhs.gov.

Thank you for the opportunity to provide comments.

6 pages of draft labeling has been withheld in full as
B(4) CCI/TS immediately following this page

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/s/

CHRISTINE G CORSER
08/16/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 8,, 2012

TO: Lucious Lim, M.D., Medical Officer
June Germain, Sr. Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 202872

APPLICANT: Bausch & Lomb Inc.
7 Giralda Farms, Suite 1001
Madison, NJ 07940
Phone #: 877-442-6925

DRUG: (b) (4) (loteprednol etabonate ophthalmic gel, 0.5%)

NME: No

THERAPEUTIC CLASSIFICATIONS: New Drug Application

INDICATION: Treatment of inflammation and pain following ocular surgery.

PDUFA: 9/29/12

ACTION GOAL DATE: 8/29/12

INSPECTION SUMMARY GOAL DATE: 7/29/12

I. BACKGROUND:

Bausch & Lomb, Incorporated submitted a New Drug Application (NDA) for (b) (4) (loteprednol etabonate ophthalmic gel, 0.5%) to support its approval for the treatment of inflammation and pain following ocular surgery. (b) (4) (loteprednol etabonate ophthalmic gel) 0.5%, was initially approved in the U.S in 1998 for treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as seasonal allergic conjunctivitis, giant papillary conjunctivitis, and acute anterior uveitis. The product (b) (4) (loteprednol etabonate ophthalmic gel) 0.5% contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The sponsor submitted the following two Phase 3 studies:

- Protocol #576, entitled “A Randomized, Multicenter, Double-Masked, Parallel-Group Clinical Safety and Efficacy Evaluation of Loteprednol Etabonate Ophthalmic Gel, 0.5% Versus Vehicle for the Treatment of Inflammation and Pain Following Cataract Surgery” and
- Protocol #577, entitled " A Randomized, Multicenter, Double-Masked, Parallel-Group Clinical Safety and Efficacy Evaluation of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Vehicle for the Treatment of Inflammation and Pain Following Cataract Surgery"

Both studies were randomized, multicenter, double-masked, parallel-group clinical safety and efficacy studies of loteprednol etabonate ophthalmic gel, 0.5% versus vehicle for the treatment of inflammation and pain following cataract surgery.

Study 576 was conducted at 20 sites in the United States. A total of 406 adult subjects at least 18 years of age were enrolled in the study. The study duration was approximately four weeks from screening to the last visit (Visit 7). Subjects were to visit the clinic seven times. Visit 1 was the Screening Visit and was to occur 14 days prior to surgery. Visit 2 was to be on the day of surgery. At Visit 3 (Postoperative Day 1), eligibility for randomization into the study was assessed. If eligible, subjects were to complete postoperative study Visits 4 through 7. Subjects were to instill one to two drops of study drug into the study eye, four times a day (QID), at approximately four hour intervals. The initial dose was to occur in the clinic, at Visit 3 (Postoperative Day 1). Study treatment was to last approximately 14 days with the last administration being the fourth dose on the day before Visit 6.

The primary objectives of this clinical study are comparison of the safety and efficacy of Loteprednol Etabonate (LE) Ophthalmic Gel, 0.5% to vehicle for the treatment of

inflammation and pain following cataract surgery. The primary endpoints of the study were the proportion of study eyes with complete resolution of anterior chamber cells at Visit 5 (Postoperative Day 8) for LE Ophthalmic Gel, 0.5% and vehicle and the proportion of study eyes with Grade 0 pain at Visit 5 (Postoperative Day 8) for LE Ophthalmic Gel, 0.5% and vehicle.

Study 577 was conducted at 20 sites in the USA and 4 investigative sites in the European Union. There were 407 subjects enrolled and randomized in this double-masked, parallel-group study. Study 577 is similar in design to Study 576.

Two domestic clinical investigators were selected for inspection. The sites were chosen on the basis of enrollment of large numbers of study subjects per site, large number of INDs in the OSI database, and absence of previous inspectional history.

II. RESULTS (by Site):

Name of CI	Protocol # and # of Subjects:	Inspection Date	Final Classification
Douglas Lorenz, D.O. 870 Seven Hills Drive Suite # 202 Henderson, NV 89052 Site #580555	Study 576/ 35 subjects	April 4 to April 25, 2012	VAI
Robert J DaVanzo, M.D. Comerstone Eye Care 307 North Lindsay Street High Point, NC 27262 Site #140100	Study 577/ 40 subjects	March 27 to March 29, 2012	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Douglas Lorenz, D.O.**

870 Seven Hills Drive
Suite # 202
Henderson, NV 89052
Site # 580555

- a. **What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.811 between April 4 and April 25, 2012.

At this site, a total of 46 subjects were screened, 35 subjects were randomized, and 35 subjects completed the study. There were no deaths. An audit of eight subjects' records was conducted. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequate adverse experience reporting. All primary efficacy endpoint data were compared with the line listings. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

- b. General observations/commentary:** The inspection of Dr. Lorenz's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for failure to conduct the study in accordance with the investigational plan and prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. For example, the following regulatory violations were observed during the inspection:

1. Failure to conduct the investigation in accordance with the investigational plan.

- a. According to the protocol, patients with $\geq$ grade 2 anterior chamber cells were to be included in the study. The review of case report forms and source documents for Subjects #33, 35 and 38 revealed that these three subjects were not enrolled in to the study because they had "too much inflammation on the study eyes".

OSI Reviewer Comments: The protocol allows exclusion of subjects who have a severe/serious ocular condition, or any other unstable condition that, in the Investigator's opinion, may preclude study treatment or follow-up. Therefore, this finding is not a regulatory violation. The observation does not impact overall data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

- b. The review of case report forms and source documents for Subject #1 (LE Ophthalmic gel 0.5%) and Subject #18 (vehicle) revealed that both subjects received the prohibited medication xibrom (an ocular non-steroidal anti-inflammatory drugs or NSAID) which should not have been given 16 days after cataract surgery during the study. Subject #1 had been also given a prohibited medication (Acular, a NSAID eye drop).

OSI Reviewer Comments: According to the investigational plan, Subject #1 received xibrom as rescue concomitant medication for lack of efficacy, and Subject # 18 received xibrom for increased inflammation of the anterior chamber. The protocol allows administering rescue therapy to

subjects who fail study treatment or develop an adverse event. Therefore, this finding is not a regulatory violation. The observation does not impact overall data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

- a. Failure to adequately document ocular pain in two subjects (Subject #13 [LE ophthalmic] and Subject #23 [Vehicle]). The protocol indicates foreign body sensation should be reported as grade 1 ocular pain. It was reported that Subjects #13 and #23 had no pain in their right eyes at Visit #3 and Visit # 6 respectively. However, the clinic visit documentation in the electronic medical records states that both subjects had intermittent foreign body sensation in their right eyes. This should have been documented as grade 1 ocular pain in both subjects.

OSI Reviewer Comments: The clinical investigator did not report foreign body sensation as grade 1 ocular pain in two subjects. However, the CI reported the finding “foreign body sensation” in the eyes to the sponsor and the observation is available in the data listings. The review division may wish to convert the reported “foreign body sensation” to grade 1 ocular pain for both subjects. Although the clinical investigator failed to adequately report grade 1 ocular pain in two subjects according to the investigational plan, which is a regulatory violation, this finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

- b. Failure to adequately document the use of concomitant medications. For all eight patients reviewed (Subjects #1, #8, #13, and #42 (LE ophthalmic), and Subjects #18, #23, #28, and #32 (Vehicle)), the reported start date of gatifloxacin ophthalmic drops is not documented in the medical records (e.g. progress notes, physician's orders, prescriptions, etc). Subject #1 (LE ophthalmic) also had two different pre-operative standing orders in the medical records, one of which indicates a prohibited medication (Acular eye drops) was administered to the subject during the study.

OSI Reviewer Comments: Although the clinical investigator failed to adequately document prophylactic use of gatifloxacin ophthalmic drop administration in the medical records, alternate source documents are available to document gatifloxacin administration. Therefore, this finding is unlikely to impact data reliability, nor did it compromise the rights, safety, and welfare of subjects in the study. The EIR shows that administration of gatifloxacin ophthalmic drops was documented in the

Concomitant Medication Log and the Concomitant Medications eCRF provided by the Sponsor.

Subjects who were expected to require treatment with systemic or ocular (either eye) corticosteroids (other than study drug), NSAIDs, mast cell stabilizers, antihistamines, or decongestants during the 18 days following cataract surgery or who used any systemic or ocular corticosteroids NSAIDs, mast cell stabilizers, antihistamines or decongestants within 14 days prior to cataract surgery should have been excluded from the study. The CI failed to exclude the only subject (Subject #1) who had received ocular steroid from the study. While the above finding is a regulatory violation, the use of concomitant medications by Subject # 1 was reported in the NDA. In addition, the finding was isolated in nature and unlikely to impact the overall reliability of efficacy and safety data from the site.

- c. Failure to adequately document a history of blepharitis in 4 subjects (Subject # 8, 18, 23, and 42). The history of blepharitis was documented only in some of the visits, and it was not clear from the documentation whether this condition was ongoing.

OSI Reviewer Comments: Although the clinical investigator failed to adequately document a history of “blepharitis” in four subjects, the observed violations are related to a few instances of inaccurate case histories, and they are not clinically significant. Given the nature of the findings, the observations do not appear to have significant impact on data reliability, on the safety and welfare of the above subjects from the site. The FDA inspector discussed the above findings with the CI during the inspection, and the clinical investigator acknowledged the violations and provided assurance to adequately maintain study records.

- c. **Assessment of data integrity:** Although regulatory violations were noted above, based on the nature of the violations, it is unlikely that these violations significantly affect overall reliability of safety and efficacy data from the site. Based on the inspectional findings provided in the EIR, data derived from Dr. Lorenz’s site are considered reliable. In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Robert J DaVanzo, M.D.

Comerstone Eye Care
307 North Lindsay Street
High Point, NC 27262
Site # 140100

- a. **What was inspected:** This inspection was conducted in accordance with compliance Program 7348.811 between March 27 and March 29, 2012.

At this site, 41 subjects were screened, 40 enrolled, and 40 subjects completed the study. For the 40 enrolled subjects a review of the informed consent documents verified that subjects signed consent forms prior to enrollment. An audit of 20 subjects' records was conducted in depth, including eligibility criteria, medical history, randomization, drug accountability records, primary efficacy endpoint, and concomitant medications. All primary efficacy endpoint data were compared with the line listings. There were no limitations to the inspection. No Form FDA 483 was issued at the conclusion of the inspection.

- b. General observations/commentary:** In general, the study was conducted appropriately. There was no evidence of under reporting of adverse events. All primary efficacy endpoint data were verified by comparison of the source documents with the line listings submitted in the NDA. No regulatory violations were noted and no Form FDA 483 was issued at the conclusion of the inspection.
- c. Assessment of data integrity:** Based on the inspectional findings above, efficacy and safety data obtained from this site can be considered reliable in support of the application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The final classification of Clinical Investigator inspection of Dr. Robert J DaVanzo is No Action Indicated (NAI). Based on the inspectional findings at this site, efficacy and safety data obtained from this site can be considered reliable in support of the application.

The final classification of Clinical Investigator inspection of Dr. Douglas Lorenz is Voluntary Action Indicated (VAI). Although regulatory violations were noted, these were not considered to have a significant impact on data reliability. Based on the inspectional findings at this site, efficacy and safety data obtained from this site can be considered reliable in support of the application.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D
Acting Team Leader
Good Clinical Practice Assessment Branch
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Susan Thompson, M.D.
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/s/

KASSA AYALEW
08/08/2012

SUSAN LEIBENHAUT
08/08/2012

SUSAN D THOMPSON
08/08/2012



IND 102,654

Bausch & Lomb, Inc.
Attn: Julie Townsend, M.P.H.
Manager, Global Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Ms. Townsend:

Please refer to the Type B, End of Phase 2 meeting between representatives of your firm and FDA on August 26, 2009. The purpose of the meeting was to discuss the development plans for the 0.5% gel (b) (4) formulation of loteprednol etabonate.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 26, 2009
START TIME: 12:05 pm
END TIME: 12:20 pm
LOCATION: White Oak, Bldg #22, Room #1313

APPLICATION: **IND 102,654**
DRUG: Loteprednol etabonate ophthalmic gel (b) (4) 0.5%

INDICATION: Treatment of inflammation and pain following ocular surgery.

SPONSOR: Bausch & Lomb, Inc.

TYPE OF MEETING: Type B - End of Phase 2

MEETING CHAIR: Wiley A. Chambers, M.D.

MEETING RECORDER: Raphael R. Rodriguez

FDA Attendees: Wiley Chambers, William Boyd, Lucious Lim, Martin Nevitt, Rima Izem, Yan Wang, Linda Ng, Sonal Wadhwa, Conrad Chen, Raphael Rodriguez

Bausch & Lomb Attendees: Don Handley, George McIntire, Brian Rohrs, Susan Schneider, Dale Usner, Julie Townsend

MEETING OBJECTIVE: To discuss the development plans for the 0.5% gel (b) (4) formulation of loteprednol etabonate.

SUMMARY OF DISCUSSION:

Responses to the applicant's Type B meeting questions were provided to Julie Townsend of Bausch & Lomb, via email dated August 21, 2009. This meeting served to clarify those responses. The Applicant's questions and the Agency's responses are as follows:

End of Phase II Questions

1. The Sponsor proposes (b) (4) to describe the dosage form in the established name for this product. Does the Agency concur with this dosage form designation?

FDA Response: No. (b) (4) is not a recognized dosage form. The viscosity specifications of the product (b) (4) are far below that of ophthalmic products labeled as ophthalmic gels. Please refer to the definition of gel in the CDER Data Standards Manual.
<http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4241B1-02-30-FDA-Topical%20Dosage%20Forms%20Definitions%20Old%20%20.pdf>

2. Bausch & Lomb intends to request a waiver from pediatric studies under PREA based on pediatric studies conducted / being conducted with 0.5% loteprednol etabonate (Study 459, Zylet vs vehicle in lid inflammation; Study 550, Zylet vs Lotemax vs tobramycin vs vehicle in blepharoconjunctivitis). This information is described in further detail in the Clinical Summary. Does the Agency concur with the appropriateness of a pediatric waiver request for this new formulation?

FDA Response: No. This proposal includes a new indication and studies in pediatric patients should be included.

3. Bausch & Lomb intends to request a waiver from conducting carcinogenicity studies based on the well-established safety profile of loteprednol etabonate. Does the Agency concur with the appropriateness of a carcinogenicity waiver request?

FDA Response: The Agency will consider a request for a carcinogenicity waiver for this product.

4. Does the Agency have any comment on the Target Product Profile for <TRADENAME> (loteprednol etabonate ophthalmic gel (b) (4) 0.5%)?

FDA Response: Labeling is a review issue and will be determined at the time of the review. There does not appear to be a rationale for a 10mL fill size bottle.

Nonclinical

5. As previously agreed upon for other loteprednol etabonate formulations, Bausch & Lomb proposes a development program relying principally on the current nonclinical safety information on loteprednol etabonate (IND 32,432 and NDA 20-583). In addition, Bausch & Lomb has conducted studies in support of the new formulation. Does the Agency concur that the proposed Phase 3 studies can be initiated based on this nonclinical development package?

FDA Response: Based on the summary reports of the repeat dose toxicity/toxicokinetic studies for the new formulation, the proposed Phase 3 clinical studies appears acceptable from the nonclinical perspective. However, the complete reports of the repeat dose ocular toxicity study and the toxicokinetic study in rabbits should be submitted for further review.

6. What additional nonclinical studies, if any, can the Agency identify at this time that would be needed to support a New Drug Application filing for this formulation?

FDA Response: *The studies appear to be adequate to support a NDA filing, but a final conclusion will be dependent on the findings during the review process.*

Clinical

7. Does the FDA agree that the rationale provided supports proceeding directly to Phase 3?

We agree.

8. Does FDA have any comments on the design of the proposed Phase 3 study as outlined in the attached draft protocol?

FDA Response:

a. *Patients from relevant demographic subsets should be studied, including both men and women, patients both above and below 75 years of age, different racial/ethnic and eye color groups of clinical interest. It is recommended that all population subsets be included in the same clinical trials rather than conducting studies in subgroups. This facilitates comparisons across subsets in the same environment.*

b. *Since the stratification is done by center, we do not recommend pooling data across small centers for the Cochran Mantel Haenzel test.*

c. *For the primary analysis, it is unclear whether you propose to use (1) the Pearson's chi-squared statistic without any adjustment for study center, or (2) the chi squared statistic from the Cochran Mantel Haenzel test stratifying for centers. We recommend that both analyses be done, but one of them should be pre-specified as primary.*

d. *You did not specify which method would be used for deriving the confidence intervals for treatment differences and p-values for primary and secondary endpoints. We recommend that you use both asymptotic methods and exact methods for pooled or stratified analyses.*

e. *Please specify the method used in your sample size calculation as well as a justification of your assumptions in this calculation about the resolution rate for the active drug and the vehicle for each of the two primary endpoints.*

f. *The wording of your primary endpoints is incorrect. In the design you propose, the primary endpoint of interest in each treatment is the proportion, not the difference of proportions. The difference of proportions is the test statistic for the hypothesis test of interest, it is not the primary endpoint for each treatment.*

g. *Additional comments may follow upon the final protocol submission and review.*

9. Does the FDA agree that the study design and plan for conduct of the proposed adequate and well-controlled Phase 3 trials, if completed successfully, will comprise appropriate evidence to support the specified labeling goals as proposed in the Target Product Profile (draft labeling)?

FDA Response: *Labeling is a review issue and will be determined at the time of the review, though the study design appears adequate for the currently proposed TPP.*

CMC

10. Does the agency agree that the physico-chemical data of this formulation support the designation as a gel (b) (4)

FDA Response: *See response to Question 1.*

11. Does the Division agree that the proposed specifications are sufficient to support Phase 3?

FDA Response: *The Table P5.1 on page 16 is different than that of page 22. Page 22 seems incomplete. In addition, it is suggested that drop size and endotoxin testing with acceptance criteria be included in the drug product specification. Particulate size limits per mL or particle size distribution testing, depending on the final claimed dosage form, should be consistent with other ophthalmic drug products. Weight loss/gain and Deliverable volume may be evaluated as a one-time study except that the former should be studied through expiry.*

12. The vendor Bausch & Lomb uses to supply ink for the primary labeling will be changing their ink technology during the development of Loteprednol Etabonate Ophthalmic Gel (b) (4) 0.5%. The new ink technology will be in place for use with the marketed product. This change will impact the labeling used in the primary stability batches. B&L plans to use the current ink technology in the first of three primary stability batches and the new ink technology in the second and third primary stability batches. Furthermore, B&L plans to perform leachable testing on stability samples labeled with the new ink technology as it is representative of the label intended to be used on the marketed product. Does the FDA concur with this approach?

FDA Response: *The approach is acceptable. However, the leachable study with the new ink should be carried on through expiry.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-102654	GI-1	BAUSCH AND LOMB PHARMACEUTICA LS INC	LOTEPREDNOL ETABONATE

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/s/

WILEY A CHAMBERS
12/31/2009

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: March 6, 2012

Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: (b) (4) (Loteprednol Etabonate Ophthalmic Gel) 0.5%

Application Type/Number: NDA 202872

Applicant/Sponsor: Bausch & Lomb

OSE RCM #: 2011-4417

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, and insert labeling for (b) (4) (Loteprednol Etabonate Ophthalmic Gel) 0.5% for vulnerabilities that may lead to medication errors in response to a request from the Division of Transplant and Ophthalmology Products (DTOP).

1.1 PRODUCT INFORMATION

- Active Ingredient: Loteprednol Etabonate
- Indication of Use: The treatment of inflammation and pain following ocular surgery
- Route of Administration: Ophthalmic
- Dosage Form: Ophthalmic Gel
- Strength: 0.5%
- Dose and Frequency of Administration: Apply 1 to 2 drops to affected eye(s) 4 times a day after surgery & continue throughout the first 2 weeks of the post-operative period
- How Supplied: 5 g in a 10 mL LDPE bottle with a controlled drop tip
- Storage: Store upright at 15°C to 25°C (59°F to 77°F)
- Container and Closure Systems: 5 g fill weight in a 10 mL LDPE bottle and a 0.5 g fill weight in a 4 mL LDPE bottle, both with (b) (4) tips and pink polypropylene caps

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 29, 2011
- Carton Labeling submitted November 29, 2011
- Insert Labeling submitted January 20, 2012

Additionally, since Alrex Ophthalmic Suspension and Lotemax Ophthalmic Suspension and Ointment are currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Alrex and Lotemax. The AERS search conducted on December 21, 2011 used the following search terms: active ingredient “Loteprednol”, trade name “Alrex” and “Lotemax,” and verbatim terms “Lotep%.” The reaction terms used include MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitation was set.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Cases excluded from the case series include those that did not describe a medication error or medication errors that were not associated with the labels or labeling of (b) (4) (e.g. adverse drug reactions not related to a medication error, product quality issues, name confusion, wrong drug, and dispensing errors unrelated to our product, and cases where cause of error could not be identified or linked to the label or labeling). See Appendix B for the ISR numbers of all excluded cases.

3 RESULTS

The AERS search identified 27 cases. Following exclusions we evaluated a total of two cases relevant to this review. Both cases involved the patients wearing contact lenses while using Lotemax. In the first case (ISR # 3465975-6), the mother of the adult patient reported her daughter suffered eye irritation as a result of wearing contact lenses while using Lotemax. She claimed the directions on the box, bottle and package insert were not bold enough and the instructions regarding the warning not to wear soft contact lenses while using this product was not clear for doctors and/or for patients. In the second case (ISR # 7465414-4), the patient experienced burning in both her eyes 3 hours after instilling the eye drop while wearing her contacts. The patient subsequently removed her contact lenses but the burning continued for an unspecified amount of time. A root cause as to why this event occurred was not provided in the narrative.

The insert labeling for (b) (4) does contain a warning in the Patient Counseling Information section advising patients not to wear soft contact lenses when using this product but no where on the container label or carton labeling is this information provided. We would recommend to the Applicant that the warning to remove soft contact lenses before using (b) (4) be included on the carton labeling

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling are unacceptable and introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented prior to approval:

A. TRADE CONTAINER LABEL - 5 G

1. Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
2. The statement of strength lacks prominence. In order to increase the prominence of the strength, we recommend moving the statement of strength to appear underneath the established name and increasing the font size.

3. The manufacturer's name is overly prominent and competes for space with the proprietary name. Decrease the prominence of the manufacturer's name on the principal display panel (PDP) and relocate it away from the top third of the PDP.
4. The route of administration statement lacks prominence. Relocate the statement "For Ophthalmic Use Only" to the principal display panel immediately following the statement of strength.
5. Ensure the lot number and expiration date are printed on the label.
6. The net quantity statement is too close to the strength. Relocate the net quantity away from the statement of strength and debold the font.
7. Remove the pink highlighting over the NDC number.

B. SAMPLE CONTAINER LABELS - 0.5 G AND 5 G

See comments A.1 to A.7 above.

C. 5 G TRADE, 0.5 G SAMPLE, AND 5 G SAMPLE CARTON LABELING

1. See comments A.1 to A.5 above.
2. The insert labeling for (b) (4) contains a warning in the Patient Counseling Information section advising patients not to wear soft contact lenses when using this product. Due to postmarketing reports showing patients have used loteprednol while wearing soft contact lenses and as a result experienced adverse drug reactions, we recommend including the statement, "Remove soft contact lenses before using (b) (4) on the carton labeling.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

Appendix A: AERS Cases Relevant to this Review (n=2)

ISR Numbers	Type of Error
3465975-6	Drug Administration Error
7465414-4	Drug Administration Error

Appendix B: AERS Cases Excluded from Further Analysis (n=25)

ISR Numbers	ISR Numbers	ISR Numbers	ISR Numbers
3255060-0	4605082-X	6547255-5	7246401-8
3263179-3	4709357-5	6730614-5	7443736-0
4088064-9	4710900-0	6653942-0	7443738-4
4144412-2	5462970-2	6704757-6	7465403-X
4567747-8	5833078-9	6714244-7	
4567749-1	6547249-X	6714263-0	
4567748-X	6135938-0	7045599-4	

4 pages of draft labeling has been withheld in full as B(4) 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/

JUNG E LEE
03/06/2012

IRENE Z CHAN
03/06/2012

CAROL A HOLQUIST
03/08/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 202872 BLA#	NDA Supplement #:S- BLA STN #
Efficacy Supplement Type SE- Proprietary Name: Established/Proper Name: Ioteprednol etabonate Dosage Form: ophthalmic gel Strengths: 0.5%	
Applicant: Bausch and Lomb Inc. Agent for Applicant (if applicable):	
Date of Application: November 29, 2011 Date of Receipt: November 29, 2011 Date clock started after UN:	
PDUFA Goal Date: September 29, 2012	Action Goal Date (if different):
Filing Date: January 28, 2012	Date of Filing Meeting: January 12, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3	
Proposed indication(s)/Proposed change(s): treatment of inflammation and pain following ocular surgery.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 102654				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: ☐ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm				
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm		X		

If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?			X	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)	X			
If yes, # years requested: 3				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?				
<i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic)			
	☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	X			

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR) If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.				

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? If yes, date consult sent to the Controlled Substance Staff: <u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff:			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? If yes, notify PeRC RPM (PeRC meeting is required)² Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?		X		
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?		X		
<i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>			X	
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			X	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): August 26, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 29, 2011 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): February 28, 2011 and December 15, 2010 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 12, 2012

BLA/NDA/Supp #: NDA 202874

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: loteprednol etabonate

DOSAGE FORM/STRENGTH: gel, 0.5%

APPLICANT: Bausch and Lomb

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: The drug in this application, loteprednol etabonate 0.5% gel, is a gel dosage form of a drug product approved in suspension and ointment dosage forms. loteprednol etabonate 0.5% ophthalmic suspension or Lotemax ® has been approved since 1998 for multiple indications (NDA 20583 suspension and NDA 200738 ointment)

On November 29, 2011 the applicant submitted an NDA for loteprednol etabonate, 0.5% gel for the treatment of Inflammation and pain following ocular surgery (b) (4)

On January 17, 2012 a teleconference was held with the applicant to discuss refuse to file issues with the indication of (b) (4) because no data was submitted to support this indication.

(b) (4)
This NDA is now for loteprednol etabonate, 0.5% gel indicated for inflammation and pain following ocular surgery.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	June Germain	Y
	CPMS/TL:	Judit Milstein	Y
Cross-Discipline Team Leader (CDTL)	William Boyd		Y

Clinical	Reviewer:	Lucious Lim	Y
	TL:	William Boyd	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Gierlie Gieser	Y
	TL:	Phillip Colangelo	Y
Biostatistics	Reviewer:	Rima Izem	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Conrad Chen	Y
	Acting TL:	Terry Miller	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Lin Qi	Y
	TL:	Balajee Shanmugam	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Denise Miller	Y
	TL:	N/A	
DDMAC Labeling Review	Reviewer:	Christine Corser	N
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:	Kassa Ayalew	Y
OSE/DMEPA (proprietary name)	Reviewer:	Jung Lee	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Karen Townsend OSE RPM Hyun Son, Safety RPM		Y
Other attendees	Martin Nevitt Jennifer Harris Rhea Llyod		Y

FILING MEETING DISCUSSION:

GENERAL	
505(b)(2) filing issues? If yes, list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments: N/A	☐ Not Applicable
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Comments:	
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
Advisory Committee Meeting needed? Comments:	☐ YES Date if known: ☒ NO ☐ To be determined
<i>If no, for an original NME or BLA application, include the</i>	Reason:

reason. For example: ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	
• Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments: none	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments: none	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: none	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: none	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments: File with comments for 74 day letter	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Renata Albrecht, MD	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List: Product Quality Microbiology: 1. Hold times in the manufacturing process were not provided. Please confirm that there are no hold times or provide the hold times with supportive stability data. 2. The (b) (4) validation study states that the product used was loteprednol etabonate ophthalmic gel; (b) (4) (b) (4) Please confirm whether the loteprednol etabonate ophthalmic gel, BAK preservative solution or other solution was used in the (b) (4) validation study. If the solution was loteprednol etabonate ophthalmic gel, then provide justification that the study supports either the (b) (4) of the BAK preservative solution and/or provide a (b) (4) validation study using the BAK preservative solution. 3. The manufacturing process for the formulation that was provided included (b) (4) additions. Please clarify if these additions are simulated in the (b) (4) <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

June Germain, M.S.	1-24-12
Regulatory Project Manager	Date
Judit Milstein	2-17-12
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

JUNE GERMAIN

02/17/2012

JUDIT R MILSTEIN

02/17/2012

NDA 202872-RPM Filing Review

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202872
Name of Drug: loteprednol etabonate ophthalmic gel, 0.5%
Applicant: Bausch & Lomb, Incorporated

Labeling Reviewed

Submission Date: November 21, 2011
Receipt Date: November 29, 2011

Background and Summary Description

This original New Drug Application (NDA) provides for the following indication: treatment of inflammation and pain following ocular surgery.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies. The resubmitted labeling will be used for further labeling discussions.

Leanna M. Kelly	January 24, 2012
Consumer Safety Officer	Date
Judit Milstein	January 25, 2012
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- ☐ There is no redundancy of information.
- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- ☐ A horizontal line must separate the HL and Table of Contents (TOC).
- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- ☒ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- ☐ Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)

- **Revision Date** (required information)

- **Highlights Limitation Statement**

- ☐ Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- ☐ The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- ☐ All text in the boxed warning is **bolded**.
- ☐ Summary of the warning must not exceed a length of 20 lines.
- ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- ☐ Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
- ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- ☐ Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”

- **Indications and Usage**

- ☒ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
[http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.h
tm.](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm)

- **Contraindications**

- ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- ☐ All contraindications listed in the FPI must also be listed in HL.
- ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- **Revision Date**

- ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- ☐ A horizontal line must separate the TOC and FPI.
- ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- ☐ Must include a brief, concise summary of critical information and cross-reference to detailed

discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- ☐ For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- ☐ For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- ☐ This section is required and cannot be omitted.
- ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

LEANNA M KELLY

02/08/2012

JUDIT R MILSTEIN

02/17/2012

NDA 202872-PLR Labeling Review

DSI CONSULT: Request for Clinical Inspections

Date: February 14, 2012

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2
Jean M. Mulinde, M.D., Acting Team Leader, GCP 2
Kassa Ayalew, M.D. Medical Officer
Division of Scientific Investigation
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: William M. Boyd, MD, Medical Officer, 301-796-0686
Division of Transplant and Ophthalmology Products

From: June Germain, Sr. Regulatory Health Project Manager, 301-796-4024
Division of Transplant and Ophthalmology Products

Subject: Request for Clinical Site Inspections

I. General Information

Application #:	NDA 202872
Applicant/ Applicant contact information:	Bausch & Lomb 7 Giralda Farms, Suite 1001 Madison, NJ 07940
	Mary Harrell Manager, Global Branded Rx Portfolio & Regulatory Strategy Group Global Pharmaceutical Regulatory Affairs 973-360-6446
Drug:	(b) (4) (loteprednol etabonate ophthalmic gel) 0.5%
NME:	No
Review Priority:	Standard 10 month review
Study Population includes < 17 years of age:	No
Is this for Pediatric Exclusivity:	No

Proposed Indication: treatment of inflammation and pain following ocular surgery

PDUFA: 9/29/12
Action Goal Date: 8/29/12
Inspection Summary Goal Date: 7/29/12

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Analyzed	Indication
DSI Choice	Study #576	406	treatment of inflammation and pain following ocular surgery
DSI Choice	Study #577	407	treatment of inflammation and pain following ocular surgery

III. Site Selection/Rationale

The clinical portion of the application has been preliminarily reviewed, and no issues have been identified to date to suggest a problem with data integrity.

An inspection is requested for at least one site for the Study #576 and at least one site for the Study #577 only as your resources permit.

Note that the highest enrollers in Study #576 are: Farrell Tyson (38 subjects), Lawrence Roel (38), and Douglas Lorenz (35).

Note that the highest enrollers in Study #577 are: Robert DaVanzo (40 subjects), Raymond Fong (36), and Bruce Silverstein (35).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ☐ Enrollment of large numbers of study subjects
- ☐ High treatment responders (specify):
- ☐ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

X Other (specify): Routine Inspections

International Inspections:

Reasons for inspections (please check all that apply):

- ☐ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☐ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Goal Date for Completion:

We request that the inspections be performed and that the Inspection Summary Results be provided by July 29, 2012. We intend to issue an action letter on this application by August 29, 2012. The PDUFA due date for this application is **September 29, 2012**.

Should you require any additional information, please contact June Germain at 301-796-4024 or William M. Boyd, MD at 301-796-0686.

Additional Information:

This is an electronic NDA submission. The Lists and Description of Investigators for the previously identified studies are found below.

16.1.4 List and Description of Investigators and Other Important Participants in the Study

Provided below is a list of sites participating in Study #576.

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
130068	Cable, Melissa, MD	(b) (6)	0001	16 (7.9%)	15 (7.4%)	31 (7.6%)
946209	DeBarge, Lawrence Raymond, MD		0001	10 (4.9%)	10 (4.9%)	20 (4.9%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
140069	Depenbusch, Michael, MD	(b) (6)	0001	10 (4.9%)	11 (5.4%)	21 (5.2%)
			0009 – Add new investigator site; add sub-investigators (b) (6) remove sub-investigators (b) (6) (b) (6)			
			0014 – Add new sub-investigator (b) (6)			
947208	Flynn, William J., MD	(b) (6)	0001	10 (4.9%)	10 (4.9%)	20 (4.9%)
170070	Ghafouri, Mohammad Cameron, MD		0002	0 (0.0%)	0 (0.0%)	0 (0.0%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
461665	Hartman, Paul, MD	(b) (6)	0001	6 (3.0%)	6 (3.0%)	12 (3.0%)
726415	Jorizzo, Paul, MD		0001	10 (4.9%)	8 (3.9%)	18 (4.4%)
504607	Katzman, Barry, MD		0001	13 (6.4%)	13 (6.4%)	26 (6.4%)
579556	Long, Daniel A., MD		0001	12 (5.9%)	12 (5.9%)	24 (5.9%)
580555	Lorenz, Douglas, DO		0001 0003 – Add new investigator site; add sub-investigator (b) (6) (b) (6) 0004 – Remove sub-investigator (b) (6) (b) (6)	17 (8.4%)	18 (8.9%)	35 (8.6%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
665474	Malhotra, Ranjan, MD	(b) (6)	0001	11 (5.4%)	10 (4.9%)	21 (5.2%)
979176	Modi, Satish, MD		0001	10 (4.9%)	12 (5.9%)	22 (5.4%)
708432	Mondzelewski, James P., MD		0001	0 (0.0%)	0 (0.0%)	0 (0.0%)
260071	Panzo, Gregory J., MD		0001	9 (4.4%)	8 (3.9%)	17 (4.2%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
752391	Protzko, Eugene E., MD	(b) (6)	0000	17 (8.4%)	17 (8.4%)	34 (8.4%)
813333	Rajpal, Rajesh K., MD		0001	1 (0.5%)	2 (1.0%)	3 (0.7%)
280072	Roel, Lawrence, MD		0001	20 (9.9%)	18 (8.9%)	38 (9.4%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
508604	Rotberg, Michael H., MD	(b) (6)	0001	12 (5.9%)	14 (6.9%)	26 (6.4%)
			0002 – Add sub-investigator (b) (6)			
			0003 – Add sub-investigators (b) (6)			
509603	Rubin, Benjamin, MD		0003	0 (0.0%)	0 (0.0%)	0 (0.0%)
976179	Tyson II, Farrell C., MD		0001	19 (9.4%)	19 (9.4%)	38 (9.4%)

16.1.4 List and Description of Investigators and Other Important Participants in the Study

Provided below is a list of sites participating in Study #577.

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
110099	Angella, Guy J., MD	(b) (6)	0003	12 (5.8%)	12 (6.0%)	24 (5.9%)
120032	Bartz-Schmidt, Karl-Ulrich, Prof. Dr. Med.		0008	6 (2.9%)	7 (3.5%)	13 (3.2%)
140100	DaVanzo, Robert J., MD		0003	20 (9.7%)	20 (10.0%)	40 (9.8%)
140118	Dua, Harminder, Prof. Dr.		0008	0 (0.0%)	0 (0.0%)	0 (0.0%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
150036	El-Harazi, Sherif M., MD, MPH	(b) (6)	0004 0008 – Add sub-investigators (b) (6)	5 (2.4%)	5 (2.5%)	10 (2.5%)
150101	Endl, Michael J., MD		0003	15 (7.3%)	14 (7.0%)	29 (7.1%)
160102	Fong, Raymond, MD		0004 0015 – Add sub-investigators (b) (6)	18 (8.7%)	18 (9.0%)	36 (8.8%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
200104	Jong, Kevin Y., MD	(b) (6)	0003 0015 – Add sub-investigator (b) (6)	14 (6.8%)	14 (7.0%)	28 (6.9%)
220105	Leonardo, Donna, DO		0004	10 (4.9%)	9 (4.5%)	19 (4.7%)
230006	Mester, Ulrich, Prof. Dr.		0008	2 (1.0%)	1 (0.5%)	3 (0.7%)
230106	Meyers, Toni Takiko, MD		0004	1 (0.5%)	0 (0.0%)	1 (0.2%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
859295	Peace, James H., MD	(b) (6)	0004 0008 – Add sub-investigator (b) (6)	12 (5.8%)	12 (6.0%)	24 (5.9%)
797349	Pendleton, Robert, MD, PhD		0003 0004 – Add sub-investigator (b) (6)	8 (3.9%)	7 (3.5%)	15 (3.7%)
290107	Shettle, Philip Lee, DO		0003	7 (3.4%)	7 (3.5%)	14 (3.4%)
712429	Shulman, David G., M D		0003	7 (3.4%)	7 (3.5%)	14 (3.4%)
863291	Silverstein, Bruce E., MD		0003	17 (8.3%)	18 (9.0%)	35 (8.6%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
490621	Silverstein, Steven M., MD	(b) (6)	0003	15 (7.3%)	14 (7.0%)	29 (7.1%)
836315	Smith, Stephen E., MD		0008	3 (1.5%)	3 (1.5%)	6 (1.5%)
742400	Sutton, James D., MD		0004	2 (1.0%)	3 (1.5%)	5 (1.2%)
992163	Taustine, Lloyd R., MD		0004	11 (5.3%)	10 (5.0%)	21 (5.2%)
554576	Treft, Robert L., MD, FACS		0004	2 (1.0%)	0 (0.0%)	2 (0.5%)
717424	Weston, Jon-Marc, MD		0003 0008 – Remove sub- investigator (b) (6)	6 (2.9%)	7 (3.5%)	13 (3.2%)

				Number of Subjects Enrolled (%)		
Site #	Principal Investigator	Subinvestigator(s)	IND Submission	LE Gel	Vehicle	Overall
511601	Wolstan, Barry J., MD	(b) (6)	0004	13 (6.3%)	13 (6.5%)	26 (6.4%)

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/s/

JUNE GERMAIN
02/15/2012