CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208219Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: January 29, 2019

To: Wendy Streight, PhD
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 208219**
LOTEMAX SM (loteprednol etabonate ophthalmic gel) 0.38%, for topical ophthalmic use

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OPDP has reviewed the proposed Carton and Container Labeling submitted for consult on June 13, 2018, for LOTEMAX SM (loteprednol etabonate ophthalmic gel) 0.38%, for topical ophthalmic use (Lotemax SM). OPDP's review is based on the October 19, 2018 proposed Carton and Container Labeling for Lotemax SM submitted by the Sponsor, also attached below. OPDP does not have any comments on the proposed Carton and Container Labeling.

OPDP's comments on the proposed Package Insert (PI) was be provided under separate cover on January 25, 2019.

Thank you for your consult. If you have any questions on our review of the proposed labeling, please contact Carrie Newcomer at 301-796-1233, or carrie.newcomer@fda.hhs.gov.

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

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/s/

CARRIE A NEWCOMER
01/29/2019 11:21:04 AM

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

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

Memorandum

Date: January 25, 2019

To: Wendy Streight, PhD
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 208219**
LOTEMAX SM (loteprednol etabonate ophthalmic gel) 0.38%, for topical ophthalmic use

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OPDP has reviewed the proposed Package Insert (PI) submitted for consult on June 13, 2018, for LOTEMAX SM (loteprednol etabonate ophthalmic gel) 0.38%, for topical ophthalmic use. OPDP's comments are provided directly below on the attached marked-up copy of the proposed PI. Our comments are based on the version of the proposed labeling located in Sharepoint on January 25, 2019.

OPDP's comments on the proposed carton and container labeling will be provided under separate cover.

Thank you for your consult. If you have any questions on our comments, please contact Carrie Newcomer at 301-796-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
01/25/2019 12:21:26 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 30, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	NDA 208219
Product Name and Strength:	Lotemax SM (loteprednol etabonate) Ophthalmic Gel 0.38%
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bausch & Lomb
FDA Received Date:	October 19, 2018
OSE RCM #:	2018-854
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for loteprednol etabonate ophthalmic gel 0.38%, the Division of Transplant and Ophthalmology (DTOP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B- N/A
ISMP Newsletters	C- N/A
FDA Adverse Event Reporting System (FAERS)*	D- N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS, CONCLUSION, AND RECOMMENDATION

The proposed container label and carton labeling are acceptable from a medication error perspective. However, we note throughout the proposed prescribing information (PI), the proprietary name placeholder, "TRADENAME", appears in place of the conditionally acceptable proprietary name, Lotemax SM[a]. Therefore, we recommend replacing the placeholder, "TRADENAME", with the conditionally acceptable proprietary name, Lotemax SM

[a] Shah M. Proprietary Name Review for Lotemax SM (NDA 208219). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 27. Panorama No. 2018- 26774336.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for loteprednol etabonate that Bausch & Lomb submitted on October 19, 2018.

Table 4. Relevant Product Information for Lotemax SM	
Initial Approval Date	N/A
Active Ingredient	Loteprednol etabonate
Indication	Treatment of inflammation and pain following ocular surgery.
Route of Administration	Ophthalmic
Dosage Form	Gel
Strength	0.38%
Dose and Frequency	Apply one drop into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.
How Supplied	5 g in a 10 mL bottle
Storage	Store upright at 15º-25ºC (59º-77ºF).

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following loteprednol etabonate labels and labeling submitted by Bausch & Lomb on October 19, 2018.

- Container label
- Carton labeling
- Professional Sample container label
- Professional Sample Carton labeling
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

Trade container label:

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

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/s/

NASIM N ROOSTA
12/30/2018 11:08:35 PM

OTTO L TOWNSEND
12/31/2018 08:29:04 AM

Clinical Inspection Summary

Date	December 6, 2018
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	William Boyd, M.D.\Clinical Team Leader Martin Nevitt, M.D.\Reviewer Wendy Streight, Ph.D.\Regulatory Project Manager
NDA#	208219
Applicant	Bausch & Lomb Incorporated
Drug	Lotemax (loteprednol etabonate (LE) ophthalmic gel 0.38%)
NME	No
Review Priority	Standard
Proposed Indication	Treatment of post-operative inflammation and pain following ocular surgery
Consultation Request Date	July 11, 2018
Summary Goal Date	December 15, 2018
Action Goal Date	February 1, 2019
PDUFA Date	February 25, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Dao and Van were inspected in support of this NDA. Based on the results of these inspections, the identical studies (Protocols 842 and 875) appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of the inspections of both Drs. Dao and Van was No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of Lotemax (loteprednol etabonate (LE) ophthalmic gel 0.38%)for the treatment of post-operative inflammation and pain following ocular surgery

Clinical inspections were requested for the following identical protocols in support of this application:

Protocols 842 and 875, "A Phase 3, Multi-Center, Double-Masked, Vehicle-Controlled, Randomized, Parallel-Group Study to Assess Loteprednol Etabonate Ophthalmic Gel, 0.38% (BID and TID) versus Vehicle Gel for the Treatment of Ocular Inflammation and Pain Following Cataract Surgery"

Protocol 842 randomized 514 subjects at 45 sites in the United States. Protocol 875 randomized 600 subjects at 43 sites in the United States.

The primary objective of these studies was to evaluate the safety and efficacy of loteprednol etabonate (LE) ophthalmic gel, 0.38% (twice per day [BID] and 3 times per day [TID]) for the treatment of postoperative inflammation and pain following cataract surgery.

The primary efficacy endpoints for these studies were:

1. the proportion of subjects with complete resolution of AC cells (cell score = 0) in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle

2. the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle

Rationale for Site Selection

The clinical sites of Drs. Dao and Van were selected for inspection as the highest enrollers in their respective studies.

III. RESULTS (by site):

Site # **Name of CI/** **Address**	**Protocol #/** **# of Subjects** **(enrolled)**	**Inspection** **Dates**	**Classification**
Site #028 **Jung Dao, M.D.** Cornea and Cataract Consultants of Arizona 3815 East Bell Road, Suite 2500 Phoenix, AZ 85032	875 Subjects: 39	30 Oct -6 Nov2018	NAI
Site #146 **Da-Thuy Van, D.O**. Texas Clinical Research Center 1100 Gulf Freeway, Suite 114 League City, TX 77573	842 Subjects: 35	16-19 Oct 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

1. Jung Dao, M.D.

At this site for Protocol 875, 43 subjects were screened, and 39 subjects were enrolled and dosed with the test article, five subjects terminated the study early, and 34 subjects completed the study. Of the five subjects terminating early, three requested termination or were lost to follow up while the two remaining subjects required rescue therapy. Informed consent was obtained appropriately from all subjects prior to any study-related activities.

The source study records of 37 subjects were reviewed for study eligibility criteria and verification of the primary efficacy endpoint. Other records reviewed included IRB and monitor correspondence, financial disclosure, training documentation, credentials, enrollment logs, source records, case report forms, inclusion/exclusion criteria, and drug accountability and storage. There was no evidence of under-reporting of adverse events.

2. Da-Thuy Van, D.O.

At this site for Protocol 842, 38 subjects were screened, and 35 subjects were randomized to the test article, nine subjects either discontinued or were withdrawn from the study, and 26 subjects completed the study. Of the nine subjects not completing the study, eight required rescue medication and one requested study termination or was lost to follow up. Informed consent was obtained appropriately from all subjects prior to any study-related activities.

Records reviewed included IRB, sponsor, and monitor correspondence, training documentation, delegation logs, screening logs, inclusion/exclusion criteria, medical records, subject diaries, and drug accountability and storage. The primary efficacy data were verifiable for all subjects. All the subject records were reviewed for the reporting of adverse events and concomitant medications.

Site records indicate that Subject (b) (6) experienced a mild case of ptosis of the right upper eye lid related to treatment with the study drug. The condition resolved without treatment or sequelae; however, this adverse event was not reported in the line listings. There was no other evidence of under-reporting of adverse events.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
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cc:
Central Doc. Rm.\NDA 208219
DTOP\Division Director\Renata Albrecht
DTOP\Team Leader\Willlam Boyd
DTOP\Reviewer\Martin Nevitt
DTOP\Project Manager\Wendy Streight
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

ROY A BLAY
12/06/2018

PHILLIP D KRONSTEIN
12/06/2018

KASSA AYALEW
12/07/2018