# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208219Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Office of Clinical Pharmacology Memo

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|---|---|
| **NDA or BLA Number** | 208219 |
| **Link to EDR** | EDR Link |
| **Applicant** | Valeant Pharmaceuticals/Bausch+Lomb |
| **Brand Name, Drug, Dosage Form and Strength** | Lotemax SM (Loteprednol etabonate ophthalmic gel 0.38%) |
| **Submission Type** | Standard |
| **Submission Date** | 04/25/2018 |
| **PUDFA Goal Date** | 02/25/2019 |
| **Proposed Indication** | Treatment of inflammation and pain following ocular surgery |
| **Dosing Regimen & Instructions** | Apply one drop of Lotemax SM 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 |
| **Associated IND** | 102654 |
| **OCP Division** | DCP IV |
| **OND Division** | DTOP |
| **OCP Review Team** | Amit A. Somani, B. Pharm., Ph. D.<br>Clinical Pharmacology Reviewer, DCP IV<br><br>Philip Colangelo, Pharm. D., Ph. D.<br>Clinical Pharmacology Team Leader, DCP IV |
| **OCP Final Signatory** | Philip Colangelo, Pharm. D., Ph. D. |

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## SUMMARY and REVIEW

This NDA 208219 is for Lotemax SM [loteprednol etabonate (LE) ophthalmic gel 0.38%] that contains 3.8 mg/g of loteprednol etabonate as a sterile preserved ophthalmic gel. The proposed indication is for the treatment of post-operative inflammation and pain following ocular surgery. LE is a corticosteroid that has been marketed in the United States (US) for over 20 years and 0.5% LE is approved by the US Food and Drug Administration (FDA) under the trade name Lotemax® for a similar indication as proposed in this current NDA submission for Lotemax SM. The marketed dosing frequency of Lotemax 0.5% is four times daily (QID). The proposed dosage regimen of Lotemax SM is one drop into the conjunctival sac of the affected eye three times daily (TID) beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

The focus of the Clinical Pharmacology review of this NDA was to assess the systemic PK exposure of LE at the proposed dosing regimen for Lotemax SM. **Study 881** characterized the PK exposure of LE in 18 healthy adult subjects following topical bilateral ocular administration of 1 drop TID of Lotemax SM for 15 days.

*Methods and Results:* PK was assessed both after single and multiple doses of Lotemax SM. Serial blood samples were collected for PK analysis of LE on following dosing on Day 1 (single dose) and Days 15 and 16 (multiple dose) The PK parameters for LE were calculated by non-compartmental methods and can be seen in **Table 1** below.

**Table 1. Summary of Lotemax SM Pharmacokinetic Parameters in Healthy Adult Subjects**

| | Study Day 1 | | | Study Day 15 | | |
|---|---|---|---|---|---|---|
| | $T_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_t$ (hr.ng/mL) | $T_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_t$ (hr.ng/mL) |
| Nquant | 18 | 18 | 8 | 18 | 18 | 18 |
| **Mean** | 0.23[a] | 0.13 | 0.15 | 0.26[a] | 0.16 | 0.35 |
| **SD** | 0.20-2.0[b] | 0.06 | 0.15 | 0.20-1.9[b] | 0.06 | 0.32 |

Source: Adapted from Study 881 PK Report

Abbreviations: $AUC_t$ = area under the curve from the time of dosing to the time of the last measurable concentration; $C_{max}$ = maximum observed drug plasma concentration; Nquant = number of subjects with quantifiable observation; SD = standard deviation; $T_{max}$ = time at which $C_{max}$ occurred.

a. Median values are presented for $T_{max}$.

b. Minimum-Maximum are presented for $T_{max}$.

*Bioanalytical:* Plasma concentrations of LE were analyzed using a validated LC/MS/MS method. The analytical ranges of the assay were validated from 0.05 to 100 ng/mL for LE and the lower limit of quantitation (LLOQ) for LE was 0.05 ng/mL. Review summary of the information from the submitted bioanalytical validation and performance reports is provided in **Table 2.**

**Table 1. Summary of the Bioanalytical Method**

| | | |
|---|---|---|
| Validation Report | Validation report provided | ☒Yes ☐No |
| | Validation report acceptable | ☒Yes ☐No |
| Performance Report | Samples analyzed within the established stability period | ☒Yes ☐No |
| | Quality control samples range acceptable | ☒Yes ☐No |
| | Sample chromatograms provided | ☒Yes ☐No |
| | Accuracy and precision of the calibration curve acceptable | ☒Yes ☐No |
| | Accuracy and precision of the quality control samples | ☒Yes ☐No |
| | Overall performance acceptable | ☒Yes ☐No |

***Reviewer's Comment:*** *Based on the findings of PK* ***Study 881****, the reviewer agrees with the Applicant's conclusion regarding systemic exposure to LE following single and multiple topical ocular dosing of one drop of* Lotemax SM *TID bilaterally for 15 days (only one dose was administered on Day 15 of the Study) in healthy adult subjects. The mean* $C_{max}$ *values were < 0.2 ng/mL on day 1 following the first dose and on day 15 following multiple doses of Lotemax SM. The mean* $AUC_t$ *were < 0.5 hr.ng/mL on day 1 following the first dose and on day 15 following multiple doses of Lotemax SM.*

## 1.1 Recommendations

The Clinical Pharmacology review team deems that systemic PK exposure to loteprednol has been adequately characterized for NDA 208219 for Lotemax SM [LE ophthalmic gel, 0.38%] at the proposed dosing regimen for the treatment of post-operative inflammation and pain following ocular surgery. The Clinical Pharmacology relevant labeling edits are currently ongoing. Apart from labeling edits, the Clinical Pharmacology review team recommends approval of NDA 208219.

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/s/

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AMIT A SOMANI
01/22/2019 10:57:35 AM

PHILIP M COLANGELO
01/22/2019 10:59:53 AM