CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210933Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Memo

NDA or BLA Number	210933
Link to EDR	EDR Link
Applicant	Kala Pharmaceuticals
Brand Name, Drug, Dosage Form and Strength	EYSUVIS; KPI-121 (loteprednol etabonate ophthalmic suspension) 0.25%
Submission Type	Standard
Submission Date	10/15/2018
PUDFA Goal Date	08/15/2019
Proposed Indication	Temporary relief of the signs and symptoms of dry eye disease.
Proposed Dosing Regimen & Instructions	Instill one to two drops of EYSUVIS into the affected eye(s) four times daily for 2 weeks.
Associated IND	117192
OCP Division	DCP IV
OND Division	DTOP
OCP Review Team	Amit A. Somani, B. Pharm., Ph. D. Clinical Pharmacology Reviewer, DCP IV Philip Colangelo, Pharm. D., Ph. D. Clinical Pharmacology Team Leader, DCP IV
OCP Final Signatory	Philip Colangelo, Pharm. D., Ph. D.

Table of Contents

SUMMARY and REVIEW

This NDA 210933 is for EYSUVIS; KPI-121 [loteprednol etabonate (LE) ophthalmic suspension] 0.25% that contains 2.5 mg/mL of loteprednol etabonate. Kala Pharmaceuticals, Inc. has developed a novel formulation of LE, designated KPI-121, using a proprietary technology known as Mucus Penetrating Particles (MPP). MPP technology utilizes (b) (4) drug particles formulated to enhance penetration through the mucous layer of the tear film. KPI-121 is an aqueous suspension (b) (4) of LE. The proposed indication is temporary relief of the signs and symptoms of dry eye disease. 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®. The marketed dosing frequency of Lotemax 0.5% is four times daily (QID). The proposed dosage regimen for EYSUVIS is one to two drops of EYSUVIS into each eye QID for 2 weeks.

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 EYSUVIS. **Study KPI-121-C-009** characterized the PK exposure of LE in 20 healthy adult subjects.

Methods: In **Study KPI-121-C-009**, two drops of EYSUVIS; KPI-121 (LE ophthalmic suspension) 0.25% were instilled QID in each eye for 15 days (Day 15 morning dose only). PK was assessed both after single and multiple doses of EYSUVIS. Serial PK samples were collected from all subjects at pre-specified time points from pre-dose to 6 hours post-dose on Day 1 and Day 15. On Day 8, a pre-dose (trough) PK sample was collected up to 30 minutes prior to ocular instillation of the day's first dose of EYSUVIS.

Bioanalytical: Plasma concentrations of LE, and the inactive metabolites*, PJ-90 and PJ-91, were analyzed using a validated LC/MS/MS method. The analytical ranges of the assay were validated from 1.00 to 1,000 ng/mL for LE and PJ-91 and the lower limit of assay quantitation (LLOQ) was 1.00 ng/mL. The analytical ranges of the assay were validated from 5.00 to 5,000 ng/mL for PJ-90 and the LLOQ was 5.00 ng/mL. The review summary of the information from the submitted bioanalytical validation and performance reports is provided in **Table 1**.

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

Results: All plasma concentrations of LE, PJ-90, and PJ-91 at every time point pre-and post-instillation of 2 drops of EYSUVIS 0.25% in each eye QID for 15 days were BLQ (Below the Limit of Quantitation). Thus, the Applicant was unable to characterize the PK parameters for LE, PJ-90, and PJ-91.

The Applicant concluded that concentrations of LE, PJ-90, and PJ-91 were not quantifiable in plasma on Days 1, 8 (trough), and 15 following topical ocular dosing of EYSUVIS QID for 15 days in healthy adult subjects.

Reviewer's Comment: *Based on the findings of PK Study KPI-121-C-009, the reviewer agrees with the Applicant's conclusion that LE, PJ-90, and PJ-91 were not quantifiable in plasma on Days 1, 8 (trough), and 15 following topical ocular dosing of 2 drops of EYSUVIS QID in each eye for 15 days (only one dose was administered on Day 15 of the Study) in healthy adult subjects.*

1.1 Recommendations

The Clinical Pharmacology team recommends approval of NDA 210933 for EYSUVIS; KPI-121 (LE ophthalmic suspension) 0.25% at the proposed dosing regimen (i.e., one to two drops of EYSUVIS into each eye four times daily for 2 weeks). The Clinical Pharmacology relevant labeling edits are ongoing.

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMIT A SOMANI
07/11/2019 10:44:13 AM

PHILIP M COLANGELO
07/11/2019 10:48:00 AM