CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210565Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Memo

NDA or BLA Number	210565
Link to EDR	EDR Link
Applicant	Kala Pharmaceuticals, Inc.
Brand Name, Drug, Dosage Form and Strength	Inveltys; Loteprednol etabonate ophthalmic suspension, 1 %
Submission Type	Standard
Submission Date	10/24/2017
PUDFA Goal Date	08/24/2018
Proposed Indication	Treatment of post-operative inflammation and pain following ocular surgery
Dosing Regimen & Instructions	Instill one to two drops into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period
Associated IND	117192
OCP Division	DCP IV
OND Division	DTOP
OCP Review Team	Amit 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.

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SUMMARY and REVIEW

This NDA 210565 is for Inveltys [loteprednol etabonate (LE) ophthalmic suspension 1%]. The proposed indication is 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 the same indication as proposed in this current NDA submission for Inveltys. The marketed dosing frequency of Lotemax 0.5% is four times daily (QID). Inveltys utilizes a novel, proprietary drug-delivery technology known as mucus penetrating particles (MPP). As per the Applicant, MPP allows for prolonged drug presence on the ocular surface and increased drug penetration into ocular tissues, and thus supports the reduced twice daily (BID) dosing frequency for Inveltys 1% compared with Lotemax 0.5% QID. The proposed dosage regimen of Inveltys 1% is one to two drops BID into the affected eye 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 of LE, and its metabolites, PJ-90, and PJ-91*****. Study KPI-121-C-008 characterized the PK exposure of LE, PJ-90, and PJ-91 in 20 healthy adult subjects following topical ocular administration of 2 drops of Inveltys 1% BID for 15 days in a randomly assigned study eye.

Methods: PK was assessed both after single and multiple doses of Inveltys 1%. Serial PK samples were collected from all subjects at pre-specified time points from pre-dose to 12 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 Inveltys 1%.

Bioanalytical: Plasma concentrations of LE, 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 5.00 to 5,000 ng/mL for PJ-90. All plasma concentrations of LE, PJ-90, and PJ-91 at every time point pre-and post-instillation of 2 drops of Inveltys 1% in one eye BID for 15 days were BLQ (Below the Limit of Quantitation). Thus, the Applicant were unable to characterize the PK parameters for LE, PJ-90, and PJ-91.

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

Reviewer's Comment: *Based on the findings of PK Study KPI-121-C-008, 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 in one eye of Inveltys 1%*

BID 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 210565 for Inveltys [loteprednol etabonate ophthalmic suspension, 1%] at the proposed dosing regimen (i.e., Instill one to two drops into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period) for the treatment of post-operative inflammation and pain following ocular surgery. The Clinical Pharmacology relevant labeling edits are ongoing.

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/s/

AMIT A SOMANI
07/31/2018

PHILIP M COLANGELO
07/31/2018