APPLICATION NUMBER:

210565Orig1s000

OTHER REVIEW(S)
**Pre-decisional Agency Information**

Memorandum

**Date:** August 9, 2018

**To:** Dheera Semidey  
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: 210565  
INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%, for topical ophthalmic use

OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on December 21, 2017, for INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%, for topical ophthalmic use. Our review is based on the version of the proposed PI and carton and container labeling that was emailed to OPDP by DTOP on August 3, 2018. OPDP’s comments are provided directly on the attached version of the proposed PI. OPDP’s comments on the proposed carton and container labeling (also attached) are provided below.

**Carton and Container**

1. OPDP is concerned that the prominence and disparate font styles of the established name and proprietary name in the presentations on the carton and container labeling do not meet the regulatory requirements. Therefore, OPDP recommends revising the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, “[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.”
2. The placement of the image of the eye within the “V” of INVELTYS represents intervening matter. We recommend that the proprietary name and the established name not be separated by placement of intervening matter that, in any way would detract, obfuscate, or de-emphasize the established name of the product, or obscure the relationship between the proprietary name and the established name. Therefore, OPDP recommends revising accordingly.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

12 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
08/09/2018
Clinical Inspection Summary

Date       June 12, 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., Clinical Reviewer
           Dheera Semiday, Regulatory Project Manager
           Division of Transplantation and Ophthalmic Products (DTOP)
NDA#        210565
Applicant  Kala Pharmaceuticals, Inc.
Drug       INVELTYS (loteprednol etabonate ophthalmic suspension) 1%
NME        No
Review Priority  Standard
Proposed Indication  Treatment of post-operative inflammation and pain following ocular surgery
Consultation Request Date  December 13, 2017
Summary Goal Date  June 15, 2018
Action Goal Date  July 1, 2018
PDUFA Date  August 24, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Martel and Milstein were inspected in support of this NDA. Based on the results of these inspections, the studies appear 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 Drs. Martel and Milstein was No Action Indicated (NAI).

2. BACKGROUND

The Applicant submitted this NDA to support the use of INVELTYS (loteprednol etabonate ophthalmic suspension) 1% for the treatment of post-operative inflammation and pain following ocular surgery.

Inspections were requested for the following protocols in support of this application:

Protocol KPI-121-C-001, “A Phase 3, Double-Masked, Randomized, Controlled Trial of KPI-121 in Postsurgical Inflammation”

Protocol KPI-121-C-005, “A Phase 3, Double-Masked, Randomized, Controlled Study to Evaluate the Safety and Efficacy of KPI-121 1% Ophthalmic Suspension in Subjects with Postsurgical Inflammation and Pain”
Protocol KPI-121-C-001

This study was conducted at 24 study sites in the U.S. randomizing 380 subjects. The primary objective of this study was to evaluate the efficacy and safety of KPI-121 ophthalmic suspension compared to placebo in subjects who experience inflammation following cataract surgery.

The primary efficacy endpoints were evaluated using hierarchical statistical testing in the following sequence:

1. the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo

2. the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo

3. the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo

4. the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo.

Protocol KPI-121-C-005

This study was conducted at 35 sites in the U.S. randomizing 520 subjects. The primary objective of this study was to evaluate the efficacy and safety of KPI-121 1% ophthalmic suspension compared to placebo in subjects who have undergone cataract surgery.

The primary endpoints were evaluated using hierarchical statistical testing in the following sequence:

1. The difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through Day 15 without receiving rescue medication prior to Day 15 for KPI-121 1% compared with vehicle

2. The difference in the proportion of study eyes with complete resolution of ocular pain (grade = 0) at postoperative Day 8 maintained through Day 15 without receiving rescue medication prior to Day 15 for KPI-121 1% compared with vehicle
**Rationale for Site Selection**

The clinical sites of Drs. Martel and Milstein were selected for inspection because of their relatively large enrollments and lack of previous inspections.

3. **RESULTS (by site):**

<table>
<thead>
<tr>
<th>Site #/ Name of CI/ Address</th>
<th>Protocol #/ # of Subjects (enrolled)</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site #112 Bernard Milstein, M.D.</td>
<td>KPI-121-C-001 Subjects: 36</td>
<td>6-19 March 2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Joseph R. Martel, M.D. Martel Eye Group 11216 Trinity River Drive Rancho Cordova, CA 95670 Ph: (916) 635-6161</td>
<td>KPI-121-C-005 Subjects: 44</td>
<td>3-5 April 2018</td>
<td>NAI</td>
</tr>
</tbody>
</table>

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

1. **Bernard Milstein, M.D.**

At this site for Protocol KPI-121-C-001, 48 subjects were screened, 36 were enrolled, and 35 subjects completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. All subjects signed and dated the consent forms prior to any study-related procedures.

The study records of 30 subjects were reviewed. Source data were compared against data listings. Records reviewed included, but were not limited to, study records, financial report forms, training records, sponsor, monitor, and IRB correspondence, IRB approvals, inclusion/exclusion criteria, randomization logs, patient histories, surgery reports, lab results, concomitant medications, progress notes, and drug accountability and storage.
The primary and secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

Discussion items included the lack of assessment of AEs for Subjects who reported itchy eyes three days after the start of treatment with the study drug. Dr. Milstein stated that these were normal surgical outcomes and per the protocol did not need to be reported.

2. Joseph R. Martel, M.D.

At this site for Protocol KPI-121-C-005, 52 subjects were screened and 44 subjects were enrolled, all of whom completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. Explicit IRB meeting attendance and voting counts were not present in IRB correspondence at the site. This observation has been referred to the OSI Compliance Oversight Branch for their assessment. The study records of 22 subjects were reviewed; these subjects signed and dated the consent forms prior to any study-related procedures.

Source data were compared against data listings. Records reviewed included, but were not limited to, staff qualifications and training records, financial disclosures, monitoring logs, sponsor, monitor, and IRB correspondence, inclusion/exclusion criteria, rescue medication status, protocol deviations, and drug accountability and storage.

The primary and secondary efficacy endpoint data were verifiable. There was no evidence of underreporting 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.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.  Acting Branch Chief for
Kassa Ayalew, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm.\NDA 210565
DTOP\Division Director\ Renata Albrecht
DTOP\Team Leader\ William Boyd
DTOP\Medical Officer\ Martin Nevitt
DTOP\Project Manager\ Dheera Semiday
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 Analyst\ Yolanda Patague
OSI\Database Project Manager\ Dana Walters
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/s/

ROY A BLAY
06/12/2018

PHILLIP D KRONSTEIN
06/12/2018

SUSAN D THOMPSON
06/12/2018
**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***

<table>
<thead>
<tr>
<th><strong>Date of This Review:</strong></th>
<th>May 2, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Requesting Office or Division:</strong></td>
<td>Division of Transplant and Ophthalmology Products (DTOP)</td>
</tr>
<tr>
<td><strong>Application Type and Number:</strong></td>
<td>NDA 210565</td>
</tr>
<tr>
<td><strong>Product Name and Strength:</strong></td>
<td>Inveltys (loteprednol etabonate) ophthalmic suspension, 1%</td>
</tr>
<tr>
<td><strong>Product Type:</strong></td>
<td>Single ingredient product</td>
</tr>
<tr>
<td><strong>Rx or OTC:</strong></td>
<td>Rx</td>
</tr>
<tr>
<td><strong>Applicant/Sponsor Name:</strong></td>
<td>Kala Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td><strong>Submission Date:</strong></td>
<td>October 24, 2017</td>
</tr>
<tr>
<td><strong>OSE RCM #:</strong></td>
<td>2017-2280</td>
</tr>
<tr>
<td><strong>DMEPA Safety Evaluator:</strong></td>
<td>Nasim Roosta, PharmD</td>
</tr>
<tr>
<td><strong>DMEPA Team Leader:</strong></td>
<td>Otto L. Townsend PharmD</td>
</tr>
</tbody>
</table>
REASON FOR REVIEW
As part of the approval process for Inveltys (loteprednol etabonate) ophthalmic suspension, 1%, the Division of Transplant and Ophthalmology (DTOP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

Kala Pharmaceuticals, Inc. submitted NDA 210565 to seek marketing approval of Inveltys (loteprednol etabonate) ophthalmic suspension, 1% indicated for the treatment of post-operative inflammation and pain following ocular surgery.

1 BACKGROUND/REGULATORY HISTORY (IF APPLICABLE) MATERIALS REVIEWED

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>C- N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>D- N/A</td>
</tr>
<tr>
<td>Other</td>
<td>E- N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>F</td>
</tr>
</tbody>
</table>

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

2 FINDINGS AND RECOMMENDATIONS
Tables 2 and 3 below includes the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

<table>
<thead>
<tr>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDENTIFIED ISSUE</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Full Prescribing Information</td>
</tr>
<tr>
<td>1. In Section 16, the lower numerals of the temperature storage range do not contain the</td>
</tr>
</tbody>
</table>
corresponding abbreviation for Celsius/Centigrade and Fahrenheit.

the Fahrenheit temperature range.
For example: “15° C” and “59° F”

Table 3: Identified Issues and Recommendations for Kala Pharmaceuticals (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>Container Labels</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDENTIFIED ISSUE</td>
</tr>
<tr>
<td>1. The trade container label for the 2.8 mL bottle is missing the linear barcode.</td>
</tr>
<tr>
<td>2. Expiration date for both 1.2 mL sample bottle and 2.8 mL trade bottle as expressed as MMYYYY.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Carton Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The 2.8 mL trade bottle carton labeling is missing the linear barcode.</td>
</tr>
</tbody>
</table>


Reference ID: 4256844
there needs to be a linear barcode on both the carton and the container.

2. Both the trade and sample carton labeling includes the statement, “Shake for 1-2 seconds.”. When numeric ranges are presented with a dash, users can overlook the dash. The statement, 1-2 seconds, could be misinterpreted as 12 seconds. Revise the statement, “Shake for 1-2 seconds.” to read, “Shake for 1 to 2 seconds.”

3 CONCLUSION

DMEPA’s evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 2 above and ask that the Division conveys the entire table to Kala Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.
Table 4 presents relevant product information for Inveltys that Kala Pharmaceuticals, Inc. submitted on October 24, 2017.

| Table 4. Relevant Product Information for Inveltys (loteprednol etabonate) 1% |
|---------------------------------|----------------------------------|
| **Initial Approval Date**       | N/A                              |
| **Active Ingredient**           | Loteprednol etabonate            |
| **Indication**                  | Indicated for the treatment of post-operative inflammation and pain following ocular surgery. |
| **Route of Administration**     | Ophthalmic                       |
| **Dosage Form**                 | Ophthalmic suspension            |
| **Strength**                    | 1%                               |
| **Dose and Frequency**          | Instill one to two drops of Inveltys™ into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. |
| **How Supplied**                | 2.8 mL in a 5 mL bottle          |
| **Storage**                     | Store upright at 15°-25°C (59°-77°F). Do not freeze. |
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 1, 2018, we searched the L:drive and AIMS using the terms, Inveltys, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any results.
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,\textsuperscript{b} along with postmarket medication error data, we reviewed the following Inveltys (loteprednol etabonate) ophthalmic suspension, 1% labels and labeling submitted by Kala Pharmaceuticals on October 24, 2017.

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

F.2 Label and Labeling Images

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/s/

NASIM N ROOSTA
05/02/2018

OTTO L TOWNSEND
05/02/2018