CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210933Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 13, 2020
To:	Derek Alberding Regulatory Project Manager **Division of Ophthalmology (DO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%
Dosage Form and Route:	for topical ophthalmic use
Application Type/Number:	NDA 210933
Applicant:	Kala Pharmaceuticals, Inc.

1 INTRODUCTION

On April 30, 2020, Kala Pharmaceutical, Inc. submitted for the Agency's review a Class 2 Resubmission to their original New Drug Application (NDA) 210933 for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use. This 505(b)(2) Application was submitted in response to the Agency's Complete Response Letter issued on August 7, 2019 due to clinical insuffiencies. With this submission, the Applicant is proposing an indication of temporary relief of the signs and symptoms of dry eye disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Divison of Ophthalmology (DO) on September 8, 2020 and September 9, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use.

2 MATERIAL REVIEWED

- Draft EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% PPI and IFU received on April 30, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on September 8, 2020.
- Draft EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% PPI and IFU received on April 30, 2020, revised by the Review Division throughout the review cycle, and received by OPDP on September 9, 2020.
- Draft EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% Prescribing Information (PI) received on April 30, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on September 8, 2020.
- Draft EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% Prescribing Information (PI) received on April 30, 2020, revised by the Review Division throughout the review cycle, and received by OPDP on September 9, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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

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

Memorandum

Date: September 23, 2020

To: Derek Alberding, Regulatory Health Project Manager
Division of Ophthalmology

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use

NDA: 210933

In response to the Division of Ophthalmology (DO) consult request dated September 9, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO on September 9, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor and received by electronic email from DO on September 9, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or Carrie.Newcomer@fda.hhs.gov.

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

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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:	August 17, 2020
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 210933
Product Name and Strength:	Eysuvis (loteprednol etabonate) ophthalmic suspension, 0.25%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kala Pharmaceuticals, Inc.
FDA Received Date:	April 30, 2020
OSE RCM #:	2018-2382
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Eysuvis (loteprednol etabonate) ophthalmic suspension, the Office of Pharmaceutical Quality (OPQ) requested that we review the proposed Eysuvis prescribing information (PI), Instructions for Use (IFU), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

Kala submitted their original proposed labels and labeling for NDA 210933 on October 15, 2018. We reviewed the PI, container labels and carton labeling and identified areas of vulnerability that may lead to medication errors.[a] On August 2, 2019, a Complete Response (CR) Letter was issued for NDA 210933 due to a lack of substantial evidence consisting of adequate and well-controlled investigations. Because the CR letter was issued, our label and labeling recommendations were not conveyed to Kala at that time. On April 30, 2020, Kala submitted their complete response to the deficiencies included in the CR letter as a resubmission of NDA 210933.

3 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
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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

[a] Roosta, N. Label and Labeling Review for Eysuvis (NDA 210933). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 12. RCM No.: 2018-2381.

Table 2 below includes the identified medication error issues with the submitted container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Kala Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Labels and Carton Labeling			
1.	The graphic that appears within the proprietary name on both the container labels and carton labeling (trade and sample) competes in prominence with the proprietary name and makes the letter 'u' appear as a letter 'i'.	To avoid medication errors and product selection errors, the proprietary name, established name, and product strength should be the most prominent information presented on the container label and carton labeling. According to 21 CFR 201.10(a), ingredient information (i.e., the proprietary name) should appear without intervening graphic matter. The graphic may be misread as the letter 'i' leading to misinterpretation of the proprietary name.	Remove or relocate the graphic that appears within the proprietary name in accordance with 21 CFR 201.10(a).
2.	The route of administration is not included on the Principal Display Panel (PDP) of the container label and carton labeling (trade and sample).	The route of administration should be included on the PDP of the container label and carton labeling to prevent wrong route of administration medication errors.	Add the route of administration "For Topical Application in the Eye" below the established name on the PDP of the container label and carton labeling (trade and sample). For example: Eysuvis (loteprednol etabonate ophthalmic suspension) 0.25% For Topical Application In The Eye
Carton Labeling			

Table 2. Identified Issues and Recommendations for Kala Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	Both the trade and sample carton labeling includes the statement, "Shake for 2-3 seconds.".	When numeric ranges are presented with a dash, users can overlook the dash. The statement, 2-3 seconds, could be misinterpreted as 23 seconds.	To address the risk of misinterpretation and for consistency with the Instructions for Use, revise the statement, "Shake for 2-3 seconds." to read, "Shake for 2 to 3 seconds."
Container Label			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors	Identify the expiration date format you intend to use. We note you intend to use the format, "MM/YYYY" for your carton labeling which could be used for your container labels as well for consistency. If this format is used, we recommend numerical characters be used. Also, for your consideration, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to

Table 2. Identified Issues and Recommendations for Kala Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			separate the portions of the expiration date.

5 CONCLUSION

Our evaluation of the proposed Eysuvis PI, IFU, container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in **Error! Reference source not found.** for the Applicant. We ask that the Division convey Table in its entirety to Kala Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found.3 presents relevant product information for Eysuvis that Kala Pharmaceuticals, Inc. submitted on April 30, 2020.

Table 3. Relevant Product Information for Eysuvis (loteprednol etabonate)	
Initial Approval Date	N/A
Active Ingredient	Loteprednol etabonate
Indication	For the short-term treatment of the signs and symptoms of dry eye disease.
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic suspension
Strength	0.25%
Dose and Frequency	One to two drops into each eye four times daily for two weeks.
How Supplied	10 mL nominal capacity white low-density polyethylene (LDPE) dropper bottle
Storage	Upright at 15°C - 25°C (59°F -77°F). Do not freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 13, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, 'loteprednol' and 'Eysuvis'. Our search identified one (1) previous review[a], and we considered our previous recommendations to see if they are applicable for this current review.

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 Eysuvis labels and labeling submitted by Kala Pharmaceuticals, Inc..

- Trade container label
- Trade carton labeling
- Professional Sample container label
- Professional Sample carton labeling
- Prescribing Information (Image not shown)
- Instructions for Use (IFU) (Image not shown)

F.2 Label and Labeling Images

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

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Clinical Inspection Summary

Date	June 14, 2019
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Wiley Chambers, M.D., Deputy Director William Boyd, M.D., Clinical Team Leader\Reviewer Dheera Semidey, Regulatory Project Manager Division of Transplant and Ophthalmology Products (DTOP)
BLA#	210933
Applicant	Kala Pharmaceuticals, Inc.
Drug	Eysuvis (loteprednol etabonate ophthalmic suspension) 0.25%
NME	No
Review Priority	Standard
Proposed Indication	Temporary relief of the signs and symptoms of dry eye disease
Consultation Request Date	November 28, 2018
Summary Goal Date	June 21, 2019
Action Goal Date	July 1, 2019
PDUFA Date	August 15, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Whitsett, Rauchman, and Nichols were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007) appear to have been conducted adequately. The final compliance classifications of the inspections of Drs. Whitsett, Rauchman, and Nichols were No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of Eysuvis (loteprednol etabonate ophthalmic suspension) 0.25% for the temporary relief of the signs and symptoms of dry eye disease.

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

KPI-121-C-002, “A Phase 2, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease”

KPI-121-C-006, “A Phase 3, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease”

KPI-121-C-007, “A Phase 3, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease”

The primary objective of these studies was to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects who have a documented clinical diagnosis of dry eye disease.

The primary efficacy endpoints in the study were:

- Comparison of mean bulbar conjunctival hyperemia scores (of the worst region of hyperemia as defined at baseline) as determined by photographic assessment at Day 29

- Comparison of mean Modified Symptom Assessment in Dry Eye (SANDE) Severity Scores over the 7 days prior to the Day 29 visit

Rationale for Site Selection

The sites of Drs. Whitsett, Rauchman, and Nichols were selected for inspection because of their relatively large enrollments for their respective studies and lack of recent inspections.

III. RESULTS (by site):

Site # Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
Site #124 **Jeffery Whitsett, M.D.** Whitsett Vision Group 1237 Campbell Road Houston, TX 77055	KPI-121-C-002 Subjects: 35	22 Jan–12 Mar 2019	NAI
Site #130 **Steven H. Rauchman, M.D.** North Valley Eye Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	KPI-121-C-006 Subjects: 95	4-8 Feb 2019	NAI
Site #133 **Kelly Kinney Nichols, O.D., Ph.D**. University of Alabama at Birmingham School of Optometry Henry Peters Building 1716 University Blvd. Birmingham, AL 35294	KPI-121-C-007 Subjects: 114	25-27 Feb 2019	NAI

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

NOTE: The co-primary efficacy endpoint of conjunctival hyperemia was based on photographs taken at the sites and forwarded to a third party ((b) (4)) for scoring. The scores were forwarded to the sponsor and not shared with the clinical sites before or after conclusion of the study. During the inspections of Drs. Whitsett and Nichols, the sponsor provided informal copies (that is, poor quality, non-certified copies) of the third party scoring of conjunctival hyperemia, which were inadequate for data verification purposes. Therefore, the co-primary efficacy endpoint of conjunctival hyperemia could not be adequately verified during the clinical investigator inspections.

1. Jeffery Whitsett, M.D.

At this site for Protocol KPI-121-C-002, 35 subjects were screened, 9 subjects failed screening, and 26 subjects were enrolled, all of whom completed the study. The informed consent forms for all subjects were reviewed, with consent being obtained appropriately prior to any study-related activities.

Source documents for 15 enrolled subjects were audited. Portions of the records of the remaining enrolled subjects were also reviewed. Records reviewed included, but were not limited to, IRB/sponsor/monitoring correspondence, financial disclosures, inclusion/exclusion criteria, randomization, study blinding, safety parameters, concomitant medications, and test article accountability.

The co-primary efficacy endpoint of the Modified Symptom Assessment in Dry Eye (SANDE) scores as presented in subject diaries was compared with the data listings and no discrepancies were noted. There was no evidence of under-reporting of adverse events

A Form FDA 483 was issued at the conclusion of the inspection. The first of two observations noted that the dates and times of administration appeared to be written by the study coordinator for at least three subjects (b) (6) rather than by the study subjects as required by protocol. The second observation regarded the failure to report an elevated intraocular pressure (IOP, 22/24 mm Hg) for one subject (b) (6). The source documentation noted that a tonometry pen was used for the measurement rather than a Goldmann tonometer, a deviation from protocol.

Reviewer's Comment: Discussion with the DTOP medical officer indicated that the tonometry pen, while useful for screening purposes, is not as accurate as a Goldmann tonometer; therefore, it is unclear whether an adverse event actually occurred. The subject's IOPs were reported as normal (16/17 mm Hg) at Visit 5 (one week later).

The perceived differences in handwriting cannot be used to support regulatory deficiencies. In addition, the single report of a potential isolated adverse event is confounded by the use of instrumentation not specified in the protocol. For these reasons, the field classification of VAI was downgraded to a final compliance classification of NAI.

2. Steven H. Rauchman, M.D.

At this site for Protocol KPI-121-C-006, 95 subjects were screened, and 36 subjects were enrolled, all of whom completed the study. The informed consent forms for 25 subjects were reviewed, with consent being obtained appropriately from these subjects prior to any study-related activities.

Source documents for 25 enrolled subjects were audited. Records reviewed included, but were not limited to, IRB/monitor correspondence, the Investigator Brochure, investigator qualifications, financial, disclosure, training records, enrollment logs, photography and image transmission, source records, CRFs, subject diaries, dosing records, corneal fluorescein staining, and test article control and accountability.

The co-primary efficacy endpoint of the Modified Symptom Assessment in Dry Eye (SANDE) scores as presented in subject diaries was compared with the data listings and no discrepancies were noted. There was no evidence of under-reporting of adverse events.

3. Kelly Kinney Nichols, O.D., Ph.D.

At this site for Protocol KPI-121-C-007, 114 subjects were screened, 101 subjects failed screening, 13 subjects were enrolled, and 12 subjects completed the study. The informed consent forms for all screened subjects were reviewed, with consent being obtained appropriately prior to any study-related activities.

Source documents for the 13 enrolled subjects were audited. Records reviewed included, but were no limited to, IRB/monitor correspondence, financial disclosure, investigator training, source worksheets, subject diaries, inclusion/exclusion criteria, randomization, protocol deviations, concomitant medications, and test article accountability and storage. The source data containing the results of the various visual examinations such as slit lamp biomicroscopy, best corrected visual acuity, corneal fluorescein staining, unanesthetized Schirmer test assessment intraocular pressure, and dilated ophthalmoscopy were compared against the electronic Case Report Forms (eCRFs) and no discrepancies were noted.

The co-primary efficacy endpoint of the Modified Symptom Assessment in Dry Eye (SANDE) scores as presented in subject diaries was compared with the data listings and no discrepancies were noted. There was no evidence of under-reporting of adverse events

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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
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:
Central Doc. Rm.\NDA 210933
DTOP\Acting Division Director\Ozlem Belen
DTOP\ Deputy Director\Wiley Chambers
DTOP\Team Leader\Reviewer\William Boyd
DTOP\Project Manager\Dheera Semidey
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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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)

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Date of This Review:	February 12, 2019
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	NDA 210933
Product Name and Strength:	Eysuvis (loteprednol etabonate) Ophthalmic Suspension, 0.25%
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Kala Pharmaceuticals, Inc.
FDA Received Date:	October 15, 2018
OSE RCM #:	2018-2381
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 Eysuvis (loteprednol etabonate) ophthalmic suspension, 0.25%, 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
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 AND RECOMMENDATIONS

Tables 2 below include the identified medication error issues with the submitted label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Kala Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling			
1.	The graphic that appears within the proprietary name on both the container labels and carton labeling (trade and sample) competes in prominence with the proprietary name and makes the letter 'u' appear as a letter 'i'.	To avoid medication errors and product selection errors, the proprietary name, established name, and product strength should be the most prominent information presented on the container label and carton labeling. According to 21 CFR 201.10(a), ingredient information (i.e., the	Remove or relocate the graphic that appears within the proprietary name in accordance with 21 CFR 201.10(a).

		proprietary name) should appear without intervening graphic matter. The graphic may be misread as the letter 'i' leading to misinterpretation of the proprietary name.	
2.	The route of administration is not included on the Principal Display Panel (PDP) of the container label and carton labeling (trade and sample).	The route of administration should be included on the PDP of the container label and carton labeling to prevent wrong route of administration medication errors.	Add the route of administration "For Topical Application in the Eye" below the established name on the PDP of the container label and carton labeling (trade and sample). For example: Eysuvis (loteprednol etabonate ophthalmic suspension) 0.25% For Topical Application In The Eye
Carton Labeling			
1.	Both the trade and sample carton labeling includes the statement, "Shake for 2-3 seconds.".	When numeric ranges are presented with a dash, users can overlook the dash. The statement, 2-3 seconds, could be misinterpreted as 23 seconds.	Revise the statement, "Shake for 2-3 seconds." to read, "Shake for 2 to 3 seconds."

4 CONCLUSION

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to Kala Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Eysuvis that Kala Pharmaceuticals, Inc. submitted on October 15, 2018.

Table 3. Relevant Product Information for Eysuvis (loteprednol etabonate)	
Initial Approval Date	N/A
Active Ingredient	Loteprednol etabonate
Indication	For temporary relief of the signs and symptoms of dry eye disease.
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic suspension
Strength	0.25%
Dose and Frequency	One to two drops into each eye four times daily for two weeks.
How Supplied	10 mL nominal capacity white low-density polyethylene (LDPE) dropper bottle
Storage	Upright at 15°-25°C (59°-77°F). Do not freeze.

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,[a] along with postmarket medication error data, we reviewed the following Eysuvis labels and labeling submitted by Kala Pharmaceuticals, Inc. on October 15, 2018.

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

F.2 Label and Labeling Images

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

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

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