CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210933Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 210933 Resubmission

Integrated Quality Assessment

From: Chunchun Zhang, ATL/Acting CMC Lead, Branch 6, ONDP/OPQ

Date: Aug-26-2020

Re: NDA 210933, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

NDA 210933, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, was recommended for approval from Product Quality perspective on Feb 22, 2019. No product quality update was submitted in the resubmission.

All the manufacturing facilities remain acceptable. An overall acceptable recommendation for all the facilities was issued on Aug 24, 2020. Therefore, NDA 210933 upholds the approval recommendation from Product Quality perspective.

CMC sections of the labeling appear identical to the approved INVELTYS (NDA 210565) except the strength. Labeling review from the Product Quality perspective is not necessary.

____Chunchun Zhang, Ph.D._____
ATL for 210933

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/

CHUNCHUN N ZHANG
08/26/2020 03:38:14 PM

QUALITY ASSESSMENT

Recommendation: Approval

NDA 210933
Review #1
Feb 22, 2019

Drug Name/Dosage Form	EYSUVIS (loteprednol etabonate ophthalmic suspension)
Strength	0.25%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Kala Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	15-OCT-2018
Amendment	17-JAN-2019

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	NA	NA
Drug Product	Chunchun Zhang	Thomas Oliver
Process	Feiyan Jin	Dan Obrzut
Microbiology	Pike Andrew	John Metcalfe
Facility	Feiyan Jin	Dan Obrzut
Biopharmaceutics	Akm Khairuzzaman	Jing Li
Regulatory Business Process Manager	Kristine Leahy	NA
Application Technical Lead	Chunchun Zhang	NA
Environmental Analysis (EA)	Chunchun Zhang	Thomas Oliver

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: Same DMFs are referenced in the approved NDA 210565

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	loteprednol etabonate drug substance (b) (4)	Adequate	7/15/2018	LoA: 3/20/2018 Reviewed by Sharon Kelly
	Type III			NA		LoA: 8/4/2017
	Type III			NA		LoA: 8/18/2017
	Type III			NA		LoA: 5/25/2017
	Type III			NA		LoA: 7/5/2017
	Type III			NA		LoA: 7/17/2017
	Type III			NA		LoA: 7/5/2017
	Type III			NA		LoA: 5/29/2018

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117192	Loteprednol etabonate ophthalmic suspension
NDA	210565	Loteprednol etabonate ophthalmic suspension, 1%

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Adequate		11/28/2018	Andrew McDOugal

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210933 for commercialization of Loteprednol etabonate ophthalmic suspension, 0.25%. The applicant has provided adequate product quality information to assure the identity, strength, purity, and quality of the proposed drug product. All information requests and review issues have been addressed. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 1/31/2019. Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. Summary of Quality Assessments

A. Product Quality Review Context

Loteprednol etabonate ophthalmic suspension, 0.25% is a sterile aqueous corticosteroid suspension for topical ophthalmic use. The applicant currently markets Loteprednol etabonate ophthalmic suspension, 1%. The proposed drug product and the marketed product have similar compositions, manufacturing process and quality controls.

Proposed Indication(s) including Intended Patient Population	Temporary relief of the signs and symptoms of dry eye disease
Duration of Treatment	Instill one to two drops into each eye four times a day for two weeks.
Maximum Daily Dose	Around 160 mg
Alternative Methods of Administration	No alternative methods

B. Quality Assessment Overview

B.1 IDENTITY	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**
Summary Evidence of Adequacy Drug substance loteprednol etabonate referenced in DMF (b) (4) was found adequate by Sharon Kelly on 7/15/2018. Two non-specific ID tests are used in the drug product specification (ICH Q6A).	
B.2 STRENGTH	
Assessment of Application Compliance	**ADEQUATE**

with Requirements	
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The strength for the proposed drug product is 0.25% while the marketed product is 1%.

B.3 PURITY	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The acceptance limits for the related substances in the proposed product remain the same as that of the approved product under NDA 210565 except for impurities (b) (4) These three impurities are proposed to be controlled (b) (4) than the approved product. Pharm/Tox reviewer Dr. Andrew McDougal has found the proposed impurities levels acceptable on 11/28/2018. The stability-indicating method is suitable for its intended purpose of quantitating the specified and unspecified degradants present in the drug product through its shelf life.

B.4 QUALITY	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The proposed drug product and the approved product have (b) (4) All the excipients are compendial. Benzalkonium chloride is the preservative.

The proposed specification for the 0.25% strength product is similar to the specification approved for the 1% strength under NDA 210565. The proposed specification for the drug product is adequate to ensure that the critical quality attributes of an ophthalmic suspension formulation are well controlled.

The biopharmaceutics reviewer Dr. Khairuzzaman recommended a PMC to develop a dissolution method for the proposed product; refer to the Biopharmaceutical review chapter for the details. However, Dr. Wiley Chambers disagreed with the proposed PMC on 1/18/2019. Therefore, the PMC was not conveyed to the applicant. A similar PMC proposed for NDA 210565 was also not pursued for the same reasons as in this instance.

The proposed commercial manufacturing process (b) (4) Final risk assessment is low for all unit operations and the applicant has provided adequate in-process controls to ensure consistent batch to batch product quality. The sterility assurance was found acceptable from quality micro perspective.

The container closure system is the same as the approved product. The only difference is the bottle size. It is a 10 mL multi-dose LDPE dropper bottle with a controlled-drop LLDPE tip, a pink HDPE cap, and a white LDPE tamper-evident overcap.

The applicant proposed a tiered stability approach as the approved product (1%) for the commercial drug product. (b) (4)

n expiration date of 30-month is granted when vials are stored at 15°C- 25°C. The physician samples when stored upright at 15°C- 25°C is granted an expiration date of 18 months. The claim for categorical exclusion based on 21 CFR 25.30 is acceptable and no extraordinary circumstances exist based on the applicant's knowledge.

B.5 BIOAVAILABILITY	
Assessment of Application Compliance with Requirements	**Not Applicable, the product is an ophthalmic suspension**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

B.6 FACILITIES	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The facilities related to the drug substance manufacturing and testing as well as the drug product manufacturing and testing are acceptable based on the satisfactory compliance history and review of manufacturing capabilities. OPF has issued an overall acceptable recommendation for all the facilities on 1/31/2019.

B.7 LABELING	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The proposed container labels meet all regulatory requirements from a CMC perspective. Review and revision of the prescribing information, and any other associated patient labeling will be conducted in collaboration with the clinical division.

C. Final Analysis of Key Product Quality Review Issues: None

D. Summary Basis for Product Quality Recommendation

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were similar to the approved product (NDA 210565) and deemed acceptable. The labels and labeling include adequate information as required. Therefore, OPQ recommends **approval** of NDA 210933 for Loteprednol etabonate ophthalmic suspension, 0.25%.

On behalf of the OPQ team,
Chunchun Zhang, Ph. D., ATL for NDA 210933

BIOPHARMACEUTICS

NDA: 210933
Drug Product Name/Strength: Loteprednol Etabonate 0.25% Ophthalmic Suspension
Route of Administration: Ophthalmic
Applicant Name: Kala Pharmaceuticals, Inc.

Background: The drug (Loteprednol etabonate) product is an ophthalmic suspension. Loteprednol etabonate was first approved in 1998 under NDA 20-583 as Lotemax® ophthalmic suspension, 0.5% (Bausch & Lomb) and, most recently, in 2013 under NDA 202-872 as Lotemax® ophthalmic gel, 0.5%. Earlier in 2018, FDA approved NDA 210565 for this drug as 1% ophthalmic suspension (Kala Pharmaceuticals, Inc.). This product has similar formulation composition but containing lower drug concentration, 0.25%. The suspended (b) (4) particles are claimed to enhance penetration of the drug through the mucous layer of the tear film and into ocular tissues.

This 505(b)(2) NDA relies in part on the FDA's findings of safety for Lotemax® 0.5% loteprednol etabonate ophthalmic suspension. The clinical package in support of this NDA includes the results of one phase 2 and two phase 3 pivotal clinical trials as the evidence of safety and efficacy.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the dissolution method used in product development, and **2)** bridging throughout product development.

Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) ***Dissolution/In Vitro Drug Release:*** *Acceptable with PMC*
   Applicant did not propose any dissolution test in their product specification. The applicant used a dissolution test [(b) (4) for the purpose of product development. The dissolution method was found to be not suitable for the proposed drug product (b) (4)

2) ***Bridging of Formulations:*** *Acceptable*
   The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the

Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 210933 for Loteprednol Etabonate 0.25% Ophthalmic Suspension, is recommended for **APPROVAL** (b) (4)

(b) (4)

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzaman, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

I concur with Dr. Akm Khairuzzaman's recommendation.
Secondary Biopharmaceutics Reviewer Name and Date:

Jing Li, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS BEING REVIEWED:

eCTD # (SND #)	Received date	Document
0000 (1)	10/15/2018	Original submission

➢ DRUG PRODUCT:

The proposed drug product is a sterile ophthalmic suspension containing (b) (4)-sized Loteprednol Etabonate (b) (4) Each milliliter of KPI-121 0.25% (Loteprednol Etabonate 0.25% Ophthalmic Suspension) contains 2.5 mg LE as the active ingredient. Inactive ingredients are glycerin, sodium citrate dihydrate, poloxamer 407, sodium chloride, edetate disodium dihydrate, citric acid, benzalkonium chloride and water for injection.

➢ *DISSOLUTION INFORMATION:*

The following dissolution method was used for the product development.

(b) (4)

The following figures provides information of the method's sensitivity with respect to (b) (4) and other quality attributes of the product.

(b) (4)

(b) (4)

[redacted]

- ***BRIDGING OF FORMULATIONS***

The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed

Reviewer's Assessment: ADEQUATE

The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.

- ***BIOWAIVER REQUEST***

None.

- **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA 210933 for Loteprednol Etabonate 0.25% Ophthalmic Suspension, is recommended for **APPROVAL** (b) (4)

Akm Khairuzzaman

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Date: 1/04/2019 12:13:28PM
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Jing Li

Digitally signed by Jing Li
Date: 1/04/2019 12:14:58PM
GUID: 508da7420002bb05ac913303b23c39bb

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 30 November 2018

TO: File-NDA 210933

FROM: Andrew Pike, PhD
Microbiology Primary Reviewer
CDER/OPQ/OPF/DMA Branch III
(240) 402-3222

THROUGH: John Metcalfe, PhD
Senior Microbiology Reviewer
CDER/OPQ/OPF/DMA Branch III

SUBJECT: NDA: 210933
Filing date: 10/15/2018
Drug Product: Loteprednol etabonate ophthalmic suspension 0.25% (EYSUVIS)
Applicant: Kala Pharmaceuticals, Inc.

A product quality microbiology review of NDA 210933 is complete, and the review recommendation is adequate.

Background

The product quality microbiology information included in NDA 210933 is substantially similar to that provided for NDA 210565 (loteprednol etabonate ophthalmic suspension 1%), which was reviewed and found adequate in microbiology review N210565MR01.docx dated 2/12/2018 and approved by the FDA on 8/22/2018. The two drug products contain the same active pharmaceutical ingredient (API) and excipients with a reduced amount of the API (b) (4) . Most of the submission documents are the same but have been updated to include the responses to microbiology information requests sent during the review of NDA 210565. (b) (4) (b) (4) (b) (4). These issues are addressed individually below.

M E M O R A N D U M

Container closure integrity testing

Loteprednol etabonate 0.25% will be packaged into 10 mL bottles, rather than the 5 mL bottles used for Loteprednol etabonate 1%. (b) (4) . Container closure integrity testing was performed by dye ingress using the same methods and acceptance criteria as described in NDA 210565. (b) (4) A full description of the methods and results are provided in NDA 210933 Section 3.2.P.2 Attachment PCL15243.

Antimicrobial effectiveness testing

(b) (4) antimicrobial effectiveness testing was performed. The drug product will use 0.01% benzalkonium chloride as a preservative, as did NDA 210565. Antimicrobial effectiveness testing was performed in accordance with USP <51> on batch 00916A1. All five compendial organisms were reduced from > (b) (4) CFU/mL to < (b) (4) CFU/mL at 7, 14 and 28 days post-inoculation, yielding satisfactory results. The antimicrobial effectiveness of BAK was confirmed down to (b) (4) % w/v, which is < (b) (4) % of the label claim for BAK, so the release specification of (b) (4) % of BAK label claim used in NDA 210565 will be used for this drug product as well. A full description of the methods and results are provided in NDA 210933 Section 3.2.P.2 Microbiological Attributes pgs. 1-2 of 4 and Section 3.2.P.2 Attachment KPI-121-T-025.

(b) (4)

M E M O R A N D U M

END

Andrew Pike

Digitally signed by Andrew Pike
Date: 12/06/2018 11:24:30AM
GUID: 59c5154001875f37b042284badb3ac00

John Metcalfe

Digitally signed by John Metcalfe
Date: 12/06/2018 12:41:14PM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

Chunchun Zhang

Digitally signed by Chunchun Zhang
Date: 2/22/2019 01:22:49PM
GUID: 51269608000064178e75377202fe6c5d

QUALITY ASSESSMENT

Recommendation: Approval

NDA 210933
Review #1
Feb 12, 2019

Drug Name/Dosage Form	EYSUVIS (loteprednol etabonate) ophthalmic suspension
Strength	0.25%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Kala Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	15-OCT-2018
Amendment	17-JAN-2019

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	NA	NA
Drug Product	Chunchun Zhang	Thomas Oliver
Process	Feiyan Jin	Dan Obrzut
Microbiology	Pike Andrew	John Metcalfe
Facility	Feiyan Jin	Dan Obrzut
Biopharmaceutics	Akm Khairuzzaman	Jing Li
Regulatory Business Process Manager	Kristine Leahy	NA
Application Technical Lead	Chunchun Zhang	NA
Environmental Analysis (EA)	Chunchun Zhang	Thomas Oliver

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: Same DMFs are referenced in the approved NDA 210565

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	loteprednol etabonate drug substance	Adequate	7/15/2018	LoA: 3/20/2018 Reviewed by Sharon Kelly
	Type III		(b) (4)	NA		LoA: 8/4/2017
	Type III			NA		LoA: 8/18/2017
	Type III			NA		LoA: 5/25/2017
	Type III			NA		LoA: 7/5/2017
	Type III			NA		LoA: 7/17/2017
	Type III			NA		LoA: 7/5/2017
	Type III			NA		LoA: 5/29/2018

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117192	Loteprednol etabonate ophthalmic suspension
NDA	210565	Loteprednol etabonate ophthalmic suspension, 1%

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Adequate		11/28/2018	Andrew McDOugal

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210933 for commercialization of Loteprednol etabonate ophthalmic suspension, 0.25%. The applicant has provided adequate product quality information to assure the identity, strength, purity, and quality of the proposed drug product. All information requests and review issues have been addressed. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 1/31/2019. Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. Summary of Quality Assessments

A. Product Quality Review Context

Loteprednol etabonate ophthalmic suspension, 0.25% is a is a sterile aqueous a corticosteroid suspension for topical ophthalmic use. The applicant currently markets Loteprednol etabonate ophthalmic suspension, 1%. The proposed drug product and the marketed product have similar compositions, manufacturing process and quality controls.

Proposed Indication(s) including Intended Patient Population	Temporary relief of the signs and symptoms of dry eye disease
Duration of Treatment	Instill one to two drops into each eye four times a day for two weeks.
Maximum Daily Dose	Around 160 mg
Alternative Methods of Administration	No alternative methods

B. Quality Assessment Overview

B.1 IDENTITY	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**
Summary Evidence of Adequacy Drug substance loteprednol etabonate referenced in DMF (b) (4) was found adequate by Sharon Kelly on 7/15/2018. Two non-specific ID tests are used in the drug product specification (ICH Q6A).	
B.2 STRENGTH	
Assessment of Application Compliance	**ADEQUATE**

with Requirements	
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The strength for the proposed drug product is 0.25% while the marketed product is 1%.

B.3 PURITY	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The acceptance limits for the related substances in the proposed product remain the same as that of the approved product under NDA 210565 except impurities (b) (4) These three impurities are proposed to be controlled (b) (4) than the approved product. Pharm/Tox reviewer Dr. Andrew McDougal has found the proposed impurities levels acceptable on 11/28/2018. The stability-indicating method is suitable for its intended purpose of quantitating the specified and unspecified degradants present it the drug product through its shelf life.

B.4 QUALITY	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The proposed drug product and the approved product have (b) (4) All the excipients are compendial. Benzalkonium chloride is the preservative.

The proposed specification for the proposed product 0.25% resembles the specification of the approved product (1%) under NDA 210565. The proposed specification for the drug product is adequate to ensure that the critical quality attributes of an ophthalmic suspension formulation are well controlled.

The biopharmaceutics reviewer Dr. Khairuzzaman has recommended a PMC to develop a dissolution method for the proposed product, refer to the Biopharmaceutical review chapter for the detailed PMC. However, Dr. Wiley Chambers disagreed with the proposed PMC on 1/18/2019. Therefore, the PMC was not conveyed to the applicant. The same PMC was not communicated to the applicant for the approved product (NDA 210565) as well.

The proposed commercial manufacturing process (b) (4) Final risk assessment is low for all unit operations and the applicant has provided adequate in-process controls for consistent batch to batch product quality. The sterility assurance was found acceptable from quality micro perspective.

The container closure system is the same as the approved product. The only difference is the bottle size. It is a 10 mL multi-dose LDPE dropper bottle with a controlled-drop LLDPE tip, a pink HDPE cap, and a white LDPE tamper-evident overcap.

The applicant proposed a tiered stability approach as the approved product (1%) for the commercial drug product. (b) (4) an expiration date of 30-month is granted when vials are stored at 15°C- 25°C. The physician samples when stored upright at 15°C- 25°C is recommended an expiration date of 18 months. The claim for categorical exclusion based on 21 CFR 25.30 is acceptable and no extraordinary circumstances exist based on the applicant's knowledge.

B.5 BIOAVAILABILITY	
Assessment of Application Compliance with Requirements	**Not Applicable, the product is an ophthalmic suspension**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

B.6 FACILITIES	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The facilities related to the drug substance manufacturing and testing as well as the drug product manufacturing and testing are acceptable based on the satisfactory compliance history and review of manufacturing capabilities. OPF has issued an overall acceptable recommendation for all the facilities on 1/31/2019.

B.7 LABELING	
Assessment of Application Compliance with Requirements	**ADEQUATE**
Identified Issues Addressed in Final Analysis (see Section C)	**None**

Summary Evidence of Adequacy

The proposed container labels meet all regulatory requirements from a CMC perspective. Review and revision of the prescribing information, and any other associated patient labeling will be conducted in collaboration with the clinical division.

C. Final Analysis of Key Product Quality Review Issues: None

D. Summary Basis for Product Quality Recommendation

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were similar to the approved product (NDA 210565) and deemed acceptable. The labels and labeling include adequate information as required. Therefore, OPQ recommends **approval** of NDA 210933 for Loteprednol etabonate ophthalmic suspension, 0.25%.

On behalf of the OPQ team,
Chunchun Zhang, Ph. D., ATL for NDA 210933

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 30 November 2018

TO: File-NDA 210933

FROM: Andrew Pike, PhD
Microbiology Primary Reviewer
CDER/OPQ/OPF/DMA Branch III
(240) 402-3222

THROUGH: John Metcalfe, PhD
Senior Microbiology Reviewer
CDER/OPQ/OPF/DMA Branch III

SUBJECT: NDA: 210933
Filing date: 10/15/2018
Drug Product: Loteprednol etabonate ophthalmic suspension 0.25% (EYSUVIS)
Applicant: Kala Pharmaceuticals, Inc.

A product quality microbiology review of NDA 210933 is complete, and the review recommendation is adequate.

Background

The product quality microbiology information included in NDA 210933 is substantially similar to that provided for NDA 210565 (loteprednol etabonate ophthalmic suspension 1%), which was reviewed and found adequate in microbiology review N210565MR01.docx dated 2/12/2018 and approved by the FDA on 8/22/2018. The two drug products contain the same active pharmaceutical ingredient (API) and excipients with a reduced amount of the API (b) (4) . Most of the submission documents are the same but have been updated to include the responses to microbiology information requests sent during the review of NDA 210565. (b) (4) (b) (4) (b) (4). These issues are addressed individually below.

M E M O R A N D U M

Container closure integrity testing

Loteprednol etabonate 0.25% will be packaged into 10 mL bottles, rather than the 5 mL bottles used for Loteprednol etabonate 1%. (b) (4) . Container closure integrity testing was performed by dye ingress using the same methods and acceptance criteria as described in NDA 210565. (b) (4) . A full description of the methods and results are provided in NDA 210933 Section 3.2.P.2 Attachment PCL15243.

Antimicrobial effectiveness testing

(b) (4) antimicrobial effectiveness testing was performed. The drug product will use 0.01% benzalkonium chloride as a preservative, as did NDA 210565. Antimicrobial effectiveness testing was performed in accordance with USP <51> on batch 00916A1. All five compendial organisms were reduced from > (b) (4) CFU/mL to < (b) (4) CFU/mL at 7, 14 and 28 days post-inoculation, yielding satisfactory results. The antimicrobial effectiveness of BAK was confirmed down to (b) (4) % w/v, which is < (b) (4) % of the label claim for BAK, so the release specification of (b) (4) % of BAK label claim used in NDA 210565 will be used for this drug product as well. A full description of the methods and results are provided in NDA 210933 Section 3.2.P.2 Microbiological Attributes pgs. 1-2 of 4 and Section 3.2.P.2 Attachment KPI-121-T-025.

M E M O R A N D U M

END

Andrew Pike

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Date: 12/06/2018 11:24:30AM
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John Metcalfe

Digitally signed by John Metcalfe
Date: 12/06/2018 12:41:14PM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

BIOPHARMACEUTICS

NDA: 210933
Drug Product Name/Strength: Loteprednol Etabonate 0.25% Ophthalmic Suspension
Route of Administration: Ophthalmic
Applicant Name: Kala Pharmaceuticals, Inc.

Background: The drug (Loteprednol etabonate) product is an ophthalmic suspension. Loteprednol etabonate was first approved in 1998 under NDA 20-583 as Lotemax® ophthalmic suspension, 0.5% (Bausch & Lomb) and, most recently, in 2013 under NDA 202-872 as Lotemax® ophthalmic gel, 0.5%. Earlier in 2018, FDA approved NDA 210565 for this drug as 1% ophthalmic suspension (Kala Pharmaceuticals, Inc.). This product has similar formulation composition but containing lower drug concentration, 0.25%. The suspended (b) (4) particles are claimed to enhance penetration of the drug through the mucous layer of the tear film and into ocular tissues.

This 505(b)(2) NDA relies in part on the FDA's findings of safety for Lotemax® 0.5% loteprednol etabonate ophthalmic suspension. The clinical package in support of this NDA includes the results of one phase 2 and two phase 3 pivotal clinical trials as the evidence of safety and efficacy.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the dissolution method used in product development, and **2)** bridging throughout product development.

Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) ***Dissolution/In Vitro Drug Release:*** *Acceptable with PMC*
   Applicant did not propose any dissolution test in their product specification. The applicant used a dissolution test (b) (4) for the purpose of product development. The dissolution method was found to be not suitable for the proposed drug product (b) (4)

2) ***Bridging of Formulations:*** *Acceptable*
   The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the

Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 210933 for Loteprednol Etabonate 0.25% Ophthalmic Suspension, is recommended for **APPROVAL** (b) (4)

(b) (4)

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzaman, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

I concur with Dr. Akm Khairuzzaman's recommendation.
Secondary Biopharmaceutics Reviewer Name and Date:

Jing Li, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS BEING REVIEWED:

eCTD # (SND #)	Received date	Document
0000 (1)	10/15/2018	Original submission

➢ DRUG PRODUCT:

The proposed drug product is a sterile ophthalmic suspension containing (b) (4)-sized Loteprednol Etabonate (b) (4). Each milliliter of KPI-121 0.25% (Loteprednol Etabonate 0.25% Ophthalmic Suspension) contains 2.5 mg LE as the active ingredient. Inactive ingredients are glycerin, sodium citrate dihydrate, poloxamer 407, sodium chloride, edetate disodium dihydrate, citric acid, benzalkonium chloride and water for injection.

➢ *DISSOLUTION INFORMATION:*

The following dissolution method was used for the product development.

(b) (4)

The following figures provides information of the method's sensitivity with respect to (b) (4) and other quality attributes of the product.

(b) (4)

(b) (4)

[redacted]

- ***BRIDGING OF FORMULATIONS***

The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed

Reviewer's Assessment: ADEQUATE

The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.

- ***BIOWAIVER REQUEST***

None.

- **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA 210933 for Loteprednol Etabonate 0.25% Ophthalmic Suspension, is recommended for **APPROVAL** [redacted] (b) (4)

Akm Khairuzzaman

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Jing Li

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Chunchun Zhang

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