CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208259Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: February 14, 2019

To: Eithu Lwin
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

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

Subject: **NDA: 208259**
ROCKLATAN™ (netarsudil and latanoprost ophthalmic solution) for topical ophthalmic use

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OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling submitted for consult on February 6, 2019, for ROCKLATAN™ (netarsudil and latanoprost ophthalmic solution) for topical ophthalmic use (Rocklatan). Our comments are based on the version of the proposed labeling located in Sharepoint on February 5, 2019, attached below. 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

(b) (4)

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.

15 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
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Clinical Inspection Summary

Date	January 9, 2019
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 Sonal Wadhwa, M.D.\Reviewer Ei Thu Lwin\Regulatory Project Manager Division of Transplant and Ophthalmology Products (DTOP)
NDA#	208259
Applicant	Aerie Pharmaceuticals, Inc.
Drug	Rocklatan (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%
NME	No
Review Priority	Standard
Proposed Indication	Indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Consultation Request Date	June 15, 2018
Summary Goal Date	January 18, 2019
Action Goal Date	March 1, 2019
PDUFA Date	March 14, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Mulaney and Dubiner were inspected in support of this NDA. Based on the results of these inspections, Protocols PG324-CS301 and PG324-CS302 appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of both Drs. Mulaney and Dubiner was No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of Rocklatan (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

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

PG324-CS301, "A prospective, double-masked, randomized, multi-center, active controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure"

PG324-CS302, “A prospective, double-masked, randomized, multi-center, active controlled, parallel-group, 3-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution 0.02% and latanoprost ophthalmic solution 0.005% in subjects with elevated intraocular pressure”

Protocol PG324-CS301 enrolled 718 subjects for the twelve-month treatment period at 58 sites in the U.S.

Protocol PG324-CS302 enrolled 750 subjects for the three-month treatment period at 60 sites in the U.S.

The primary objectives of Protocol PG324-CS301 were to evaluate the ocular hypotensive efficacy of netarsudil 0.02% and latanoprost 0.005% ophthalmic solution once daily (QD) relative its active components, netarsudil 0.02% QD and latanoprost 0.005% QD, over a 3-month period and to evaluate the ocular and systemic safety of netarsudil/latanoprost over a 12-month period.

The primary efficacy measure for Protocol PG324-CS301 was IOP at 08:00, 10:00 and 16:00 hours at Week 2, Week 6, and Month 3, as measured by Goldmann applanation tonometry.

The primary objectives of Protocol PG324-CS302 were to evaluate the ocular hypotensive efficacy and ocular and systemic safety of netarsudil 0.02% and latanoprost 0.005% ophthalmic solution QD relative to each of its active components, netarsudil 0.02% QD and latanoprost 0.005% QD, over a 3-month period.

The primary efficacy measure for Protocol PG324-CS302 was IOP at 08:00, 10:00 and 16:00 hours at Week 2, Week 6, and Month 3, as measured by Goldmann applanation tonometry.

Rationale for Site Selection

The clinical sites of Drs. Mulaney and Dubiner were selected for inspection as they were high enrollers in their respective studies.

III. RESULTS (by site):

Site # Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #155 **Jay Mulaney, M.D.** Central Florida Eye Associates 814 Griffin Road Lakeland, FL 33805	PG324-CS301 Subjects: 50	15-21 Aug 2018	NAI
Site #228 **Harvey Dubiner, M.D.** Clayton Medical Center 1000 Corporate Center Drive, Suite 120 Morrow, GA, 30260	PG324-CS302 Subjects: 34	23-30 Oct 2018	NAI

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

1. Jay Mulaney, M.D.

At this site for Protocol PG324-CS301, 60 subjects were screened, ten subjects were screen failures, 50 subjects were randomized to the test article, 12 subjects discontinued the study, and 38 subjects completed the study. Informed consent was obtained appropriately from all 60 subjects prior to any study-related activities.

Other records reviewed included IRB, sponsor, and monitor correspondence, financial disclosure, delegation logs, inclusion/exclusion criteria, the safety endpoint for ten randomly selected subjects, protocol deviations, and test article accountability and storage. Three serious adverse events (SAEs) were reported by the CI. The CI did not attribute these SAEs to the use of the test article, a lack of causality with which the sponsor agreed (see Table 1 below). These SAEs appear to have been reported to the sponsor in compliance with the protocol and were reported to the FDA as evidenced by their presence in the line listings. The primary efficacy endpoint was verifiable for all 38 completed subjects. There was no evidence of under-reporting of adverse events.

Table 1: SAEs at Site #155

Subject number	Onset date	Nature of SAE	Severity	Causality	Action taken and Outcome
(b) (6)		Cellulitis-left leg	Severe	**NOT RELATED** to the test article.	Subject was **hospitalized** for more than 24 hours. Subject recovered.
		Abdominal Pain	Moderate	**NOT RELATED** to the test article.	Subject was **hospitalized** for more than 24 hours. Subject recovered.
		Gall bladder-cholecystitis	Moderate	**NOT RELATED** to the test article.	Subject was **hospitalized** for more than 24 hours. Subject recovered.

2. Harvey Dubiner, M.D.

At this site for Protocol PG324-CS302, 39 subjects were screened, five subjects failed screening, 34 subjects were enrolled, one subject withdrew consent, and 33 subjects completed the study. Informed consent was obtained appropriately from all subjects prior to any study-related activities. The source documents of 19 subjects were reviewed in their entirety.

Records reviewed included IRB, CRO, and sponsor correspondence, training records, financial disclosure documents, inclusion/exclusion criteria, laboratory results, and test article accountability and storage. The primary efficacy endpoint was verifiable for all enrolled subjects. There was no evidence of under-reporting 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:

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Phillip Kronstein, M.D.
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
Branch Chief
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cc:
Central Doc. Rm.\NDA 208259
DTOP\Division Director\Renata Albrecht
DTOP\Team Leader\Willlam Boyd
DTOP\Reviewer\Sonal Wadhwa
DTOP\Project Manager\Ei Thu Lwin
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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/s/

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PHILLIP D KRONSTEIN
01/09/2019 12:02:09 PM

KASSA AYALEW
01/09/2019 12:08:40 PM

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:	July 31, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	NDA 208259
Product Name and Strength:	Rocklatan (Netarsudil and Latanoprost) Ophthalmic Solution, 0.02%/0.005%
Product Type:	Multi-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aerie Pharmaceuticals, Inc.
FDA Received Date:	PI submission May 14, 2018, Carton and Container submission July 25, 2018
OSE RCM #:	2018-1022
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 Rocklatan (Netarsudil and Latanoprost) Ophthalmic Solution, 0.02%/0.005%, the Division of Transplant of 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

Table 2 below includes 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 Aerie Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

Container Labels	
1.	(b) (4)

	(b) (4)		
2.	The trade container label is missing the linear barcode.	The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product selection and administration errors.	Per 21 CFR 201.25, the linear barcode must appear on the product container label (as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)).
Carton Labeling			
1.	The strength on the Principal Display Panel (PDP) is too small and hard to read compared to other product identifying information.	To avoid product selection errors, the strength must be displayed clearly and prominently on the PDP.	In accordance with 21 CFR 201.15(a)(6), increase the size of the product strength on the PDP.
2.	(b) (4)		

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 the Aerie Pharmaceuticals, Inc. so that

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

recommendations are implemented prior to approval of this NDA. We have found the proposed Prescribing Information (PI) to be acceptable from a medication error prospective.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Rocklatan that Aerie Pharmaceuticals, Inc. submitted on May 14, 2018.

Table 4. Relevant Product Information for Rocklatan	
Initial Approval Date	N/A
Active Ingredient	Netarsudil and latanoprost
Indication	Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	0.02%/0.005%
Dose and Frequency	One drop in affected eye(s) once daily in the evening. The Maximum Daily Dose is not yet determined (b) (4)
How Supplied	2.5 mL fill in a 4 mL low density polyethylene (LDPE) bottle with a (b) (4) dropper tip and (b) (4) white (b) (4) cap
Storage	2-8°C (36-46°F) (b) (4) protected from light

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,[c] along with postmarket medication error data, we reviewed the following Rocklatan labels and labeling submitted by Aerie Pharmaceuticals, Inc. on July 25, 2018.

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

F.2 Label and Labeling Images

(b) (4)

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

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/s/

NASIM N ROOSTA
07/31/2018

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