

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208259Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Complete Response

**NDA 208259
Review # 1
Feb 8, 2019**

Drug Name/Dosage Form	<i>Netarsudil/ Latanoprost Ophthalmic Solution</i>
Strength	<i>0.02%/0.005%</i>
Route of Administration	<i>Topical ophthalmic</i>
Rx/OTC Dispensed	<i>Rx</i>
Applicant	<i>Aerie Pharmaceuticals, Inc.</i>
US agent, if applicable	<i>NA</i>

SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Original</i>	<i>5/14/2018</i>
<i>Amendment</i>	<i>6/15/2018</i>
<i>Amendment</i>	<i>6/25/2018</i>
<i>Amendment</i>	<i>10/17/2018</i>
<i>Amendment</i>	<i>11/13/2018</i>
<i>Amendment</i>	<i>1/8/2019</i>
<i>Amendment</i>	<i>1/11/2019</i>
<i>Amendment</i>	<i>1/15/2019</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Monica Cooper	Su (Suong) Tran
Drug Product	Shrikant Pagay	Chunchun Zhang
Microbiology	David Bateman	Julie Nemecek
Biopharmaceutics	Akm Khairuzzaman	Jing Li
Process	Feiyan Jin	Dan Obrzut
Facility	Feiyan Jin	Dan Obrzut
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Shrikant Pagay	Chunchun Zhang

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status ¹	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	7/12/2018	LoA: 8/18/2015 Sharon Kelly
	Type III		NA		LoA: 10/27/2017	
	Type III		NA		LoA: 9/21/2017	
	Type III		NA		LoA: 4/18/2018	
	Type III		NA		LoA: 9/19/2017	
	Type III		NA		LoA: 9/27/2017	
	Type III		NA		LoA: 9/19/2017	
	Type III		NA		LoA: 9/20/2017	
	Type III		NA			

¹NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	113064	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		12/13/2018	Maria Rivera



QUALITY ASSESSMENT



CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality micro, manufacturing process, and biopharmaceutics aspects.

The compliance status of the drug product manufacturing facility (b) (4) (b) (4) was found withhold based on previous inspection performed ending (b) (4) (b) (4). The most recent inspection was conducted ending (b) (4). During this inspection, corrective actions to previous FDA 483 were verified. This inspection was initially classified as NAI. However, the OAI classification has not been finally downgraded to VAI or NAI yet at this time. Thus, this facility is recommended to be withheld. Therefore, OPF has issued an overall recommendation of “Withhold” on 2/6/2019. In agreement with the above recommendation, NDA 208259 is recommended for **Complete Response** from Product Quality perspective. Once the facilities status update from OPF becomes available, a final recommendation from OPQ will be documented in an addendum.

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 Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.
Duration of Treatment	One drop in the affected eye(s) once daily in the evening See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance, Latanoprost, is a light yellow (b) (4) oil. The drug substance referenced in DMF (b) (4) was found adequate by Sharon Kelly on 7/12/2018.

The other drug substance, Netarsudil dimesylate, is a light yellow to white powder. A (b) (4) month retest period is appropriate.

ii. Drug Product Quality Summary

Netarsudil and latanoprost. 0.02%/ 0.005% ophthalmic solution is sterile, preserved and packaged in a 4 mL multi-dose LDP (b) (4) wit (b) (4) tip and polypropylene screw cap. The fill volume is 2.5 mL.

Both netarsudil and latanoprost were previously approved in separate NDAs at the same concentrations (0.02% and 0.005%) provided in this submission. All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. benzalkonium chloride (BAC) is the preservative in the formulation. The drug product specification includes tests for appearance, identity, assay, impurities (specified, unspecified and total), BAC assay, pH, osmolality, sterility, particulate matter. The proposed impurities limits are found acceptable by the pharm/tox reviewer Dr. Maria Rivera on 12/13/2018. All analytical methods are described in reasonable detail and have been adequately validated. The applicant has performed extractable and leachable studies, no reportable extractable or leachable was detected. A risk assessment on the elemental impurity was performed and indicate the results are lower than PDE.

The applicant has submitted one registration batch at th (b) (4) L scale and two batches at the (b) (4) L scale using the commercial process and packaging. The proposed commercial scale (b) (4) L. Data through 12 months was available at 5°C at upright and horizontal orientations. Stability data for six months at 25°C/40% RH and three months at 30°C/35%RH are provided. All the quality attributes remain within the proposed specifications. Therefore, the expiration date of 24 months is granted when stored at 2 °C- 8 °C.

The storage statement is “Protect from light. Store at 2°C - 8°C (36°F - 46°F).” and will be finalized at the OND’s labeling meeting.

The proposed drug product manufacturing process consists (b) (4)

(b) (4)
(b) (4)
(b) (4) During the NDA review several information requests regarding to critical process parameters and hold time for (b) (4) etc. were conveyed to and addressed by the applicant. The overall information regarding the manufacturing process provided in the NDA submission and subsequent amendments was found acceptable. The drug product

i (b) (4) It is found acceptable from quality micro perspective. (b) (4)

Biopharmaceutics reviewer Dr. Akm Khairuzzaman has found the dissolution method and bridging of formulations are not needed as the proposed drug product is an aqueous ophthalmic solution.

OPF has issued a withhold recommendation for the drug product manufacturing site (b) (4) from the outcome of the previous inspection ending (b) (4). The final recommendation from the recent inspection ending (b) (4) is not available at this time. All the other facilities are acceptable based on the profile. Therefore, the current overall recommendation of “withhold” was entered for the NDA into Panorama by OPF on 2/6/2019. Once the final recommendation becomes available, an addendum from OPF will be documented.

C. Special Product Quality Labeling Recommendations (NDA only)
NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure ¹ Process parameters Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Endotoxin Pyrogen	Formulation Container closure ¹ Process parameters Scale/equipment	L		L	No endotoxin testing required.
Assay (API), stability	Formulation Container closure ¹ Raw materials	L		L	

Assay (preservative)	Formulation Container closure ¹ Process parameters Scale/equipment	L	(b) (4)	L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure ¹ Process parameters Scale/equipment	M		L	
pH	Formulation Container closure ¹ Process parameters Scale/equipment	L		L	
Particulate matter	Formulation Container closure ¹ Process parameters Scale/equipment	M		L	

¹Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

This NDA is recommended for **Complete Response** from the Product Quality Perspective.

On behalf of the OPQ team
Chunchun Zhang, Ph.D. ATL for NDA 208259

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BIOPHARMACEUTICS

NDA: 208259; 505(b)(2)

Drug Product Name/Strength: Netarsudil/latanoprost ophthalmic solution, 0.02% & 0.005%

Route of Administration: Ophthalmic

Applicant Name: Aerie Pharmaceuticals Inc.

Submission Date: 05/14/2018

Background: Aerie Pharmaceuticals is seeking approval for netarsudil/latanoprost ophthalmic solution, 0.02% & 0.005% under the 505(b)(2) path, relying upon FDA's previous findings of safety and efficacy for the approved listed drug products: Rhopressa (NDA-208254) and Xalatan (NDA-020597). The drug product is to be administered by applying one drop of the ophthalmic solution in the affected eye(s) once daily for the treatment of elevated intraocular pressure in patients with glaucoma. The proposed drug product is a sterile multi-dose aqueous ophthalmic formulation with preservative, benzalkonium chloride (0.02%). Other inactive ingredients in the formulation composition are mannito (b) (4), boric acid (b) (4), sodium hydroxide (b) (4), water for injectio (b) (4). The proposed formulation composition of this fixed dose combination product is identical to that o (b) (4) Rhopress (b) (4) (b) (4) except for the benzalkonium chloride which was increased from 0.015% to 0.02% in this product.

The clinical package in support of this NDA includes the results of 2 randomized and controlled clinical trials in patient with open-angle glaucoma and ocular hypertension.

REVIEW SUMMARY

The *Biopharmaceutics* review focused on the evaluation of the adequacy of Biopharmaceutics-related information/data, as summarized below:

- 1) Dissolution Method and Acceptance Criteria(on):** Not relevant. The proposed drug product is an aqueous ophthalmic solution and drug release is not an attribute to measure.
- 2) Bridging of Formulations:** Not relevant. There was no change in the formulation composition between the phase 3 and commercial formulations. Manufacturing process, and/or manufacturing site between the proposed commercial product and registration batches are also the same. Additionally, the change in the amount of benzalkonium chloride in this formulation (0.015% to 0.02%) compared to that of the Listed Drug Product is supported by the pivotal clinical studies.
- 3) Biowaiver Request:** None.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 208259 for Netarsudil/latanoprost ophthalmic solution, 0.02% & 0.005% is recommended for **APPROVAL**.



**QUALITY A QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics**



SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

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

Secondary Biopharmaceutics Reviewer Name and Date:

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



Akm
Khairuzzaman

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Jing
Li

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MICROBIOLOGY

Product Background:

NDA: 208259

Drug Product Name / Strength: Netarsudil/latanoprost ophthalmic solution 0.02% / 0.005%, multi-dose bottle.

Route of Administration: Ophthalmic

Applicant Name: Aerie Pharmaceuticals, Inc.

Manufacturing Site:

(b) (4)

Method of Sterilization

(b) (4)

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: The drug product i (b) (4) filled into 4 mL bottles.

List Submissions Being Reviewed: May 14, 2018, June 25, 2018, July 25, 2018,

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None identified.

Supporting Documents: None.

S Drug Substance

Since the drug product is sterilized during the drug product manufacturing process, then the drug substance will not be reviewed.

Not Applicable

Reviewer's Assessment: The drug product is (b) (4) filling into the bottles. The drug substance will not be reviewed.

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** A clear sterile, preserved, ophthalmic multi dose isotonic solution in a low-density polyethylene bottle with white (b) (4) (b) (4) polyethylene dropper tip and polypropylene screw cap.
- **Drug product composition:**

Ingredient	Content per mL
Netarsudil mesylate	0.2 mg
Latanoprost, USP	0.0 (b) (4) mg
Mannitol, USP	(b) (4)
Boric acid, NF	
Benzalkonium chloride, NF	
Sodium hydroxide, NF	
Water for Injection, USP	

- **Description of container closure system:**

Component	Description	Manufacturer
Bottle	Sterile 4 mL LDPE (b) (4) (b) (4)	(b) (4)
Dropper	Sterile (b) (4) white (b) (4) dropper	
Cap	Sterile (b) (4) PP white (b) (4)	

Adequate

Reviewer's Assessment:
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

(b) (4)

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability summary and conclusions)

The Proposed expiry is 24 months. The applicant noted that antimicrobial effectiveness testing will be conducted on at least one registration stability lot at the end of the

proposed shelf life but will not be conducted for commercial product as per Pre-NDA meeting held on August 18, 2017 (postapproval-stability-bl.pdf, page 2).

Adequate

Reviewer's Assessment:

The applicant's proposed 24 month expiry is acceptable based on provided microbial data.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(3.2.P.8.2 Post approval stability protocol and stability commitment)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP<71>	Sterile

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 5 °C ± 3 °C

Test	Time (Months)							
	0	3	12	24	27	30	36	48
Sterility	X		X	X	X	X	X	X

The applicant notes that the 27, 30, 36 and 48 testing points may be revised or deleted once the final expiry period has been established.

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Adequate

Reviewer's Assessment:

The applicant provided an acceptable stability program for microbial testing.

P.8.3 Stability Data

(3.2.P.8.3 Stability data)

The applicant provided sterility data and antimicrobial data at 6 months stored at accelerated conditions of 25 °C ± 2 °C and 40% RH ± 5%. Also, long term sterility data and antimicrobial data were provided up to 12 months at 5 °C ± 3 °C.

Adequate

Reviewer's Assessment:

The applicant provided acceptable microbiology stability data.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Not Applicable
Reviewer's Assessment:

A.2.1 Materials of Biological Origin

Not Applicable
Reviewer's Assessment:

A.2.2 Testing at Appropriate Stages of Production

Not Applicable
Reviewer's Assessment:

A.2.3. Viral Testing of Unprocessed Bulk

Not Applicable
Reviewer's Assessment:

A. 2.4 Viral Clearance Studies

Not Applicable
Reviewer's Assessment:

R Regional Information

Executed Batch Records

The batch records confirm that validate manufacturing processes were used for th

(b) (4)

Adequate
Reviewer's Assessment:
The applicant provided detailed batch records for batches 272042, 272051 and 272061, which used the described manufacturing processes.

Comparability Protocols

None Provided

Not Applicable

Reviewer's Assessment:**2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q)
MODULE 1****2.A. Package Insert****(1.14.1.3 Draft labeling text)**

Storage 2-8 °C

Route of administration: One drop in eye daily.

Container: 4 mL multiple dos (b) (4)

The package insert states to protect from light, store at 2-8 °C, and that during shipment the bottle may be maintained at temperatures up to 40°C for no more than 14 days.

At the August 18, 2017 pre-NDA meeting the Agency agreed that one registration lot will be stored for 24 months at 5 °C ± 3 °C and then stored for an additional six weeks at 25 °C ± 3 °C, 60% RH ± 5% RH to support the use of the product at conditions of 2- 25 °C. The results from this study will be provided in a prior-approval supplement to request a change to the label to allow for storage of the product at 2-25 ± 3 °C while in use by the patient (stability-summary-bl.pdf, page 19). The applicant provided the protocol which will be followed (p-00036.pdf), sterility and antimicrobial testing will be conducted once removed from 5 °C ± 3 °C and at 42 days. The bottles will be stored horizontal.

Adequate**Reviewer's Assessment:**

The applicant provided acceptable instructions for the storage of the drug product.

Post-Approval Commitments:**Not Applicable****Reviewer's Assessment:**

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

David Bateman, Ph.D.

October 24, 2018

Secondary Reviewer Name and Date:

Julie Nemecek, Ph.D.

I concur. October 31, 2018



David
Bateman

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Julie
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NDA 208259 (Netarsudil/Latanoprost Ophthalmic Solution, 0.02%/0.005%)

Product Quality Assessment (Addendum #1 to IQA #1)

From: Chunchun Zhang, ATL/Acting CMC Lead, Branch 3, ONDP

Date: Feb-28-2019

Re: Approval recommendation from product quality perspective

Drug substance, drug product, biopharmaceutics, manufacturing process and quality micro reviewers have recommended approval of NDA 208259 as documented in IQA #1.

As documented in this Addendum, the drug product manufacturing facility (b) (4) is classified as NAI based on the recent inspection ending (b) (4). (b) (4) The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on Feb 26, 2019. Therefore, NDA 208259 is recommended for **APPROVAL** from the Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

Chunchun Zhang, Ph.D.
ATL for 208259



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Chunchun
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