

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208254Orig1s000

PRODUCT QUALITY REVIEW(S)



QUALITY ASSESSMENT



Recommendation: Approval

**NDA 208254
Review # 1
Oct 30, 2017**

Drug Name/Dosage Form	<i>Rhopressa (Netarsudil ophthalmic solution)</i>
Strength	<i>0.02%</i>
Route of Administration	<i>Topical</i>
Rx/OTC Dispensed	<i>Rx</i>
Applicant	<i>Ariel Pharmaceuticals, Inc.</i>
US agent, if applicable	<i>NA</i>

SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Original</i>	<i>2/28/2017</i>
<i>Amendment</i>	<i>6/6/2017</i>
<i>Amendment</i>	<i>6/20/2017</i>
<i>Amendment</i>	<i>7/10/2017</i>
<i>Amendment</i>	<i>8/2/2017</i>
<i>Amendment</i>	<i>8/22/2017</i>

Quality Review Team

DISCIPLINE	REVIEWER
Application Technical Lead	Chunchun Zhang
Drug Substance	Sithamalli Chandramouli
Drug Product	George Lunn
Microbiology	Wendy Tan
Biopharmaceutics	NA
Process	Steve Rhieu
Facility	Rose Xu
Regulatory Business Process Manager	Kristine Leahy
ORA Lead	Caryn McNabb
Laboratory (OTR)	NA
Environmental Assessment (EA)	Raanan Bloom

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status ¹	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	NA		LoA: 1/25/2016
	Type III		NA		LoA: 1/25/2016	
	Type III		NA		LoA: 5/22/2016	
	Type III		NA		LoA: 1/25/2016	
	Type III		NA		LoA: 2/1/2016	
	Type III		NA		LoA: 4/7/2016	
	Type III		NA		LoA: 1/25/2016	
	Type II		NA		LoA: 11/17/2015	

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	This product during IND development

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			



QUALITY ASSESSMENT



CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Satisfactory information and response have been submitted to support the quality of the drug substance, drug product, process and quality micro aspects.

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 10-27-2017.

Therefore, NDA 208254 is recommended for approval from Product Quality perspective.

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 elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
Duration of Treatment	NA
Maximum Daily Dose	About (b) (4) mg (one drop in each affected eye once daily in the evening).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance is Netarsudil mesylate, a new molecular entity. Molecular weight is 453.53 g/mol (free base) and 645.74 g/mol (dimesylate salt). It is a light yellow to white powder.

[Redacted] (b) (4)

The specifications for starting materials, reagents and solvents are appropriate. The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control.

The primary packaging material consists of an [Redacted] (b) (4)

[Redacted]

The primary stability data support the proposed retest period of (b) (4) months at (b) (4) °C.

ii. Drug Product Quality Summary

Netarsudil ophthalmic solution, 0.02% is a sterile, clear, aqueous solution preserved with benzalkonium chloride in a 4 mL multi-dose ophthalmic low density polyethylene plastic dropper bottles with a 2.5 mL fill with an (b) (4) plastic dropper tip and white polypropylene cap.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, pH, osmolality, identity, assay, impurities, chiral purity, benzalkonium chloride, particulates, sterility, and antimicrobial effectiveness. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated.

Batch analyses are provided for 11 batches manufactured by (b) (4) on a (b) (4) scale (the commercial scale of (b) (4)). All batches complied with the proposed specification.

Stability data is updated to twenty-four months at long term storage 5°C, 12 months at 25°C/40% RH, and 6 months at 30°C/65% RH for four 2.5 mL fill registration batches with upright and inverted orientations at the scale of (b) (4). There is no trend observed for all the test parameters when the drug products were stored at long term storage condition (5°C). No leachables were observed from the study conducted for 6 batches for 18 months at 5°C, 6 months at 25°C/40% RH, and 30°C/65% RH. These results support both the expiration dating period and storage statement listed below. The applicant has provided one time in-use stability in the Amendment dated on 6/20/2017 to support the storage for 6 weeks at 2-25°C after opening.

The storage statement is: “Store at 2°C-8°C (36°F-46°F) until opened. After opening, the product may be kept at 2°C-25°C (36°F-77°F) for up to 6 weeks.”

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 ³	H	Formulation includes a preservative; sterilization has been validated; facilities were currently	H	Post-approval stability protocol ² will test sterility.
Endotoxin Pyrogen	Formulation Container closure ¹ Process parameters Scale/equipment	L	This is a topical product and therefore does not require testing for endotoxin.	L	No endotoxin testing required.
Assay (API), stability	Formulation Container closure ¹ Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	Formulation Container closure ¹ Process parameters Scale/equipment	L	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	L	AET performed on routine stability.
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure ¹ Process parameters Scale/equipment	M	4 mL natural LDPE bottle with 2.5 mL fill volume; drop size study and the minimal weight loss observed support deliverable volume.	L	
Osmolality	Formulation Container closure ¹ Process parameters Scale/equipment	L	Clinically relevant specification; stability studies show no significant change.	L	
pH	Formulation Container closure ¹ Process parameters Scale/equipment	L	Buffered formulation; No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	Formulation Container closure ¹ Process parameters Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>.	M	

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

2 Post-approval stability protocol provides for testing of all quality attributes.

MICROBIOLOGY

Product Background

NDA: 208254

Drug Product Name / Strength: Rhopressa™, Netarsudil mesylate 0.02%
Ophthalmic Solution

Route of Administration: Topical Ophthalmic Instillation

Applicant Name: Aerie Pharmaceuticals, Inc., 2030 Main St., Suite 1500,
Irvine, CA 92614

Manufacturing Site: [REDACTED] (b) (4)

Method of Sterilization: [REDACTED] (b) (4)

Review Recommendation: Adequate

Review Summary:

- The submission is **recommended** for approval on the basis of sterility assurance.
- The product is [REDACTED] (b) (4)
- There is currently no deficiency identified from the information submitted.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
02/28/2017*	02/28/2017	N/A	2/28/2017
08/30/2016	08/30/2016	N/A	2/28/2017
07/10/2017	07/10/2017	N/A	07/10/2017
08/02/2017	08/02/2017	N/A	08/03/2017

***Resubmission**

Highlight Key Outstanding Issues from Last Cycle: None

Remarks: This is an eCTD submission

Concise Description Outstanding Issues Remaining: None

Supporting Documents: None

List Number of Comparability Protocols (ANDA only): N/A. This is a NDA

S Drug Substance

Reviewer's Assessment:

(b) (4)

Therefore, microbiology review will not be conducted for drug substance.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – A clear, sterile, topical multi-dose aqueous ophthalmic formulation preserved with benzalkonium chloride. A Rho kinase inhibitor indicated for treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.
- **Drug product composition** –

Ingredient	Function	0.2 mg/mL	
		Content per mL	Quantity (% w/v)
Netarsudil mesylate	API	0.2 (b) (4)	0.02 (b) (4)
Mannitol			
Boric acid			
Benzalkonium chloride	Preservative	(b) (4)	0.015
Sodium hydroxide	pH Adjuster	As needed	As needed
WFI	(b) (4)	q.s	q.s.
Total		1 mL	100%

- **Description of container closure system – P.7.**

Configuration	Component	Description	Manufacturer
2.5 mL fill in a 4 mL bottle	Bottle	4 mL white (b) (4) round (b) (4) LDPE (b) (4)	(b) (4)
	Tip	15 mm white (b) (4) dropper tip (b) (4)	(b) (4)
	Closure	15 (b) (4) white cap, extended (b) (4) tip, (b) (4) polypropylene (b) (4)	(b) (4)
	Seal		(b) (4)

Exhibit Batches: (b) (4) (P.5.4) – Batches 228511/228512 – (b) (4)
 228521/228522/228523 – (b) (4) and 242811, 242812 – (b) (4)

Finished lot # 228512, 228522/228523 and 242812 met the release specification of USP <71> (P.5.4).

Reviewer's Assessment: Adequate

P.7 Container Closure

See P.1.

Reviewer's Assessment: Adequate

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(P.8.1)

Proposed Expiry: 24 months

The proposed expiry of 24 months when stored at 2°C – 8°C is from testing up to 18 months. Extrapolated projections indicated that the product is stable beyond 24 months. The BAK preservative tested at up to (b) (4) were within specifications.

Reviewer's Assessment: Adequate

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(P.8.2)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
AET	USP <51>	Meets requirements
Sterility	USP <71>	Meets USP <71>

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

Stability storage conditions: 25° ± 2°C/60% ± 5%RH

Test	Time (Months)						
	0	12	24	27*	30	36	48
AET	N/A	X	X	X	X	X	X
Sterility	X	X	X	X	X	X	X

*Test beyond 24 M is optional and 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.

Note to reviewer: The applicant has committed to conduct AET at expiry. Therefore, the DMA standard deficiency for commitment to test AET at expiry for preserved ophthalmic eye drops will not be issued.

Reviewer's Assessment: *Adequate*

P.8.3 Stability Data

(P.8.3 pages 33-36, 47-50, 54-57)

Stability data are provided for vials placed in the upright and inverted position.

Accelerated: 25±2°C/ 40% ± 5% RH: up to 6 months

AET for BAK – met acceptance criteria

BAK content: (b) (4) %

Sterility – Pass (Meets USP <71>)

Tested at initial and 6 M

Long Term: 5°C±3°C: up to 18 months

AET for BAK – Pass (met requirements for Cat 1 USP <51>)

BAK content (b) (4) %

Sterility – Pass (Meets USP <71>)

Tested at initial and 12 M

Results above are from Batches 228512, 228522/228523 and 242812 (2.5 mL fill)

Results for other batches with (b) (4) fills are provided but not included here as the subject application is only for 2.5 mL fill.

Reviewer's Assessment: *Adequate*

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: *N/A*

A.2.1 Materials of Biological Origin

Reviewer's Assessment: *N/A*

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: *N/A*

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: *N/A*

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: *N/A*

R Regional Information

Executed Batch Records

Executed lot #(s): 22101, 22850, 24281

The batch records confirm that the Executed Batches 22101, 22850, and 24281 were produced using validated [REDACTED] (b) (4) processes. The records indicated that [REDACTED] (b) (4)

Note to reviewer: The executed batches [REDACTED] (b) (4)

Reviewer's Assessment: Adequate

The executed batch records indicated that the manufacturing procedures as described in the submission were followed.

Comparability Protocols

R.2 Comparability Protocol – No CP was included in the application.

Reviewer's Assessment: N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

- **Post-dilution/constitution hold time**

PACKAGE INSERT

(1.14.1.3 package insert)

Storage temperature: 2°-8°C (36° to 46°F). The product may be kept at 2°C – 25°C (36°F – 77°F) after opening.

Route of administration: topical ophthalmic instillation

Container: Single-patient vial, multiple-dose, preserved.

Reconstituted/Further Diluted Drug Product

Ready to use eye drops, no reconstitution or further dilution required.

Note to reviewer: The applicant states [REDACTED]

(b) (4)

[REDACTED] The applicant states that the product can be stored at 2°C-25°C after opening, therefore the study is proposed.

Reviewer's Assessment: Adequate

Post-Approval Commitments:

Reviewer's Assessment: N/A

List of Deficiencies:

There are currently no deficiencies identified from the information submitted.

Primary Microbiology Reviewer Name and Date:

Wendy Tan, Ph.D.

Microbiologist

CDER/OPQ/OPF/DMA/BII

August 03, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Nandini Bhattacharya, Ph.D.

Microbiologist

CDER/OPQ/OPF/DMA/BII

Aug 03, 2017



Wendy
Tan

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OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 208254	Established/Proper Name: Rhopressa™ (netarsudil ophthalmic solution)
Applicant: Aerie Pharmaceuticals, Inc.	Dosage Form: solution
Submission Type: 505(b)(1)	Strength(s): 0.02%
Chemical Type: NME	Cross Referenced Applications: IND 113064

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		The NDA is fileable from the OPQ perspective.
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		X	

A. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS
<p><i>The NDA provides for netarsudil ophthalmic solution, 0.02% for for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The proposed dosing regimen is 1 drop in the affected eye(s) once daily in the evening.</i></p>

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

B. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 AND 25.15(d) been provided?	X			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	X			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	X			
FACILITY INFORMATION					
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	X			<p>Drug substance manufacturer: (b) (4)</p> <p>Current status: AC from last inspection on (b) (4)</p> <p>Drug Product manufacturer: (b) (4)</p> <p>Current status: OAI from last inspection on (b) (4)</p> <p>The inspection is tentatively scheduled on (b) (4)</p>
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	X			
DRUG SUBSTANCE INFORMATION					
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

B. FILING CONSIDERATIONS					
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 			X	Note: this application is 505(b1) and the proposed drug product is a topical solution.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>			X	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.			X	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			X	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			X	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?			X	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X		
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X			Executed batch records for all drug product used in the phase 3 and registration batches are provided. No executed batch records for drug substances are provided.
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			X	
17.	For Biotech Products, is sufficient information provided in compliance with 21 CFR 610.9 and 601.2(a)?			X	

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NDA FILING REVIEW

Drug Substance:

Netarsudil mesylate drug substance is a new molecular entity as a light yellow to white powder packaged in (b) (4). The specification is provided below.

Table 1 Netarsudil Mesylate Drug Substance Specification

Test	Acceptance Criteria	Analytical Procedure
Description	Light yellow to white powder.	Visual (AD017 TST)
Identification of AR-13324 IR ¹ HPLC ¹	Conforms to reference standard spectrum. The retention time of the main peak in the sample chromatogram corresponds to that of the main peak in the standard chromatograms.	FTIR (USP <197>; AD002 TST) HPLC (AD130 TST)
Assay (anhydrous basis, % w/w)	(b) (4)	HPLC (AD130 TST)
Chromatographic Purity (% w/w) ² (b) (4)	(b) (4)	HPLC (AD130 TST)
Total Impurities ³ (b) (4)		HPLC (AD072 TST)
		IC (AD121 TST)
		GC-HS (AD082 TST)
Residual Solvents (ppm) ⁴ (b) (4)		GC-HS (AD137 TST)
Water Content (% w/w)		GC (AD142 TST) Karl Fischer (USP <921>; AD004 TST)

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NDA FILING REVIEW

Test	Acceptance Criteria	Analytical Procedure
Elemental Impurities ($\mu\text{g/g}$) ¹ (b) (4)	(b) (4)	ICP-MS (USP <233>, <232>; AD077 TST)
Microbial Bioburden Test Total Aerobic Count Total Yeasts & Mold Count Absence of objectionable organisms ⁴ (b) (4)	(b) (4)	Microbiological Examination (USP <61>, <62>; AD050 TST)
		HPLC (AD073 TST)
		GC (AD106 TST)
Residue on Ignition (% w/w) ^{1,3}		(USP <281>; AD114 TST)

NMT = Not More Than; CFU = Colony Forming Units

1. (b) (4)
2. Structures and names of impurities are provided in Section 3.2.S.3.2.
3. Total Impurities includes all impurities observed at or above (b) (4) % in the chromatographic purity test. (b) (4) is not included in the Total Impurities.
4. Objectionable organisms: *Staphylococcus aureus*; *Pseudomonas aeruginosa*; *Bacillus subtilis*; *Candida albicans*; *Aspergillus brasiliensis*; *Escherichia coli*; *Salmonella enterica*; *Burkholderia cepacia*.
5. As proposed in the Type B Pre-NDA CMC Meeting, IND 113064, Serial Number 0088, these tests will be (b) (4)

Section 3.2.S.4.5.

Drug Product:

Netarsudil ophthalmic solution 0.02% is a clear, sterile, preserved, isotonic solution at approximately pH 5. The formulation is packaged in a multi-dose LDPE bottles with (b) (4) LDPE dropper tips and white PP screw caps. In the NDA submission 2.5 mL fill size in 4 mL bottles for commercial and (b) (4) fill size in 4 mL bottle may be used as a professional sample presentation in the future.

Drug product composition:

OFFICE OF PHARMACEUTICAL QUALITY
NDA FILING REVIEW

Table 1 **Composition and Components of Netarsudil Ophthalmic Solution 0.02%**

Component	Function	Netarsudil Concentration: 0.2 mg/mL	
		Quantity per mL (mg)	Quantity (% w/v)
Netarsudil mesylate	Active Ingredient	0.2 (b) (4)	0.02
Mannitol	(b) (4)	(b) (4)	(b) (4)
Boric acid			(b) (4)
Benzalkonium chloride			Preservative
Sodium hydroxide ³	pH Adjuster	as needed	as needed
Water for Injection	(b) (4)	q.s.	q.s.
Total		1 mL	100%
(b) (4)			

Drug product specification:

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NDA FILING REVIEW

Table 1 Specifications for Netarsudil Ophthalmic Solution 0.02%

Test	Acceptance Criteria
Description	Clear solution, free of visible particles
pH	(b) (4)
Osmolality (mOsm/kg)	(b) (4)
Identification of AR-13324 by UV ¹	UV Spectrum of sample is essentially the same as that of AR-13324 reference standard
Identification of AR-13324 by Retention Time ¹	The retention time of the AR-13324 peak corresponds to that of the AR-13324 reference standard
Assay: AR-13324 content (% LC)	(b) (4)
(b) (4)	(b) (4)
Any unspecified degradation product	(b) (4)
Total degradation products ³ (% w/w)	(b) (4)
Benzalkonium Chloride (% LC)	(b) (4)
Particulate Matter	NMT 50 particles/mL ≥10 μm NMT 5 particles/mL ≥25 μm NMT 2 particles/mL ≥50 μm
Sterility	Meets requirements of USP <71>
Antimicrobial Effectiveness Test ⁴	Meets Requirements of USP <51> for Category 1 product

UV = Ultraviolet detection LC = Label Claim NMT = Not More Than NLT = Not Less Than

(b) (4)

The proposed commercial scale is (b) (4). Twelve months stability data when stored at long term storage condition (5°C) and 6 months at accelerated condition (25°/40%RH) are provided for three registration batches with the scale of (b) (4). The stability studies were performed at upright and inverted orientations. The applicant performed leachable/ extractable, photostability and freeze-thaw study. The shelf-life of 24 months is proposed. The applicant also proposed the drug product can be stored at 2-25°C for up to 6 weeks once the bottle is opened. The in-use stability to support this statement will be submitted during the review cycle.

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NDA FILING REVIEW

Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
Sterility	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipment • Site 	<ul style="list-style-type: none"> • Non-sterile unit(s) 	4	5	4	80		H
Assay (API), stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	(b) (4)	3	2	2	6	(b) (4)	L
Assay (preservative)	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipment • Site 	<ul style="list-style-type: none"> • Lack of effectiveness through shelf-life 	1 (Release) 1 (Stability)	1	1	1	Preservative: BAC (b) (4)	L
Assay (b) (4)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters 	<ul style="list-style-type: none"> • Decrease in potency 					Not used	L

OFFICE OF PHARMACEUTICAL QUALITY
NDA FILING REVIEW

	<ul style="list-style-type: none"> Scale/equipment Site 							
Uniformity of Dose (Fill Volume/Deliverable volume)	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Insufficient dose 	4	3	1	12	(b) (4) L	
Osmolality	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Irritation Edema 	2	2	2		Osmolality testing is performed (DP specifications).	L
pH-	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Irritation Particulate formation due to delamination (with high pH) 	4	4	1	16	pH testing is performed (DP specifications).	L
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Irritation Embolism 	3	5	4	60	Tested in DP specifications.	M
Leachable extractables	<ul style="list-style-type: none"> Formulation Container closure 	<ul style="list-style-type: none"> Generation of impurities 					Test data provided	

OFFICE OF PHARMACEUTICAL QUALITY
NDA FILING REVIEW

	<ul style="list-style-type: none"> • Process parameters • Scale/equipment • Site 		4	4	1	16		M
Appearance (Color/turbidity)	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipment • Site 		3	3	1	9		L



Chunchun
Zhang

Digitally signed by Chunchun Zhang
Date: 4/03/2017 07:26:28PM
GUID: 5126960800064178e75377202fe6c5d



OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208254 Submission Type: 505(b)(1)

Established/Proper Name:
Rhopressa™ (netarsudil
ophthalmic solution)

Applicant: Aerie
Pharmaceuticals, Inc.

Letter Date: Aug 29, 2016

Dosage Form: solution

Chemical Type: NME

Stamp Date: Aug 30, 2016

Strength: 0.02%

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NDA 208254 was not evaluated for filing from OPQ perspective as it was withdrew on Oct. 27, 2016.
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?			Facility comment was sent to the applicant on 10/2/2016. Drug product comments were sent to the applicant on 10/6/2016. Detailed comments are attached in the end of this filing review.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Meeting minutes for IND 113064 in DARRTS dated on 3/10/2014
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) ²	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other _____	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	(b) (4)
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.		Excipients	<input checked="" type="checkbox"/>	<input type="checkbox"/>
37.		Microbial	<input checked="" type="checkbox"/>	<input type="checkbox"/>
38.	Unique analytical methodology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input type="checkbox"/>	To be determined during review
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input type="checkbox"/>	To be determined during review
44.	Continuous Manufacturing	<input type="checkbox"/>	<input type="checkbox"/>	To be determined during review
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	<input type="checkbox"/>	To be determined during review
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other _____	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The applicant requests exemption from an environmental assessment based on the categorical exclusion listed in 21 CFR 25.31(a).

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
2.	<p>Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <p><input type="checkbox"/> Drug Substance</p> <p><input type="checkbox"/> Drug Product</p> <p><input type="checkbox"/> Appendices</p> <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <p><input type="checkbox"/> Regional Information</p> <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
FACILITY INFORMATION					
3.	<p>Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list:</p> <p><input type="checkbox"/> Name of facility,</p> <p><input type="checkbox"/> Full address of facility including street, city, state, country</p> <p><input type="checkbox"/> FEI number for facility (if previously registered with FDA)</p> <p><input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person.</p> <p><input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and</p> <p><input type="checkbox"/> DMF number (if applicable)</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Drug substance manufacturer: (b) (4)</p> <div style="background-color: #cccccc; height: 40px; width: 100%;"></div> <p>Drug Product manufacturer: (b) (4)</p> <div style="background-color: #cccccc; height: 40px; width: 100%;"></div>
4.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p> <p>For BLA:</p> <p><input type="checkbox"/> Is a manufacturing schedule provided?</p> <p><input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG SUBSTANCE INFORMATION					
5.	<p>For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
	<p>information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 			
DRUG PRODUCT INFORMATION				
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are 	☒	<input type="checkbox"/>	<input type="checkbox"/>

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	bacterial challenge studies submitted to support the proposed filter? <input type="checkbox"/> Control of Excipients <input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <input type="checkbox"/> Reference Standards or Materials <input type="checkbox"/> Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <input type="checkbox"/> Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Note: this application is 505(b1) and the proposed drug product is topical solution.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Executed batch records for all drug product used in the phase 3 and registration batches are provided. No executed batch records for drug substances are provided.
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Are the following information available for Biotech Products: <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples				

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

Summary or Product Quality

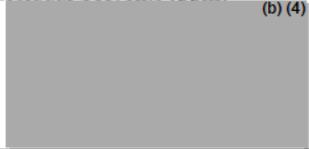
The NDA provides for netarsudil ophthalmic solution, 0.02% for for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The proposed dosing regimen is 1 drop in the affected eye(s) once daily in the evening.

Drug Substance:

Netarsudil mesylate drug substance is a new molecular entity as a light yellow to white powder packaged in [REDACTED] ^{(b) (4)} The specification is provided below.

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FILING REVIEW

Table 1 **Netarsudil Mesylate Drug Substance Specification**

Test	Acceptance Criteria	Analytical Procedure
Description	Light yellow to white powder.	Visual (AD017 TST)
Identification of AR-13324 IR ¹ HPLC ¹	Conforms to reference standard spectrum. The retention time of the main peak in the sample chromatogram corresponds to that of the main peak in the standard chromatograms.	FTIR (USP <197>; AD002 TST) HPLC (AD130 TST)
Assay (anhydrous basis, % w/w)	(b) (4)	HPLC (AD130 TST)
Chromatographic Purity (% w/w) ²  Total Impurities ³	(b) (4)	HPLC (AD130 TST)
	(b) (4)	HPLC (AD072 TST)
	(b) (4)	IC (AD121 TST)
	(b) (4)	GC-HS (AD082 TST)
Residual Solvents (ppm) ⁴ 	(b) (4)	GC-HS (AD137 TST) GC (AD142 TST)
Water Content (% w/w)	(b) (4)	Karl Fischer (USP <921>; AD004 TST)

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FILING REVIEW

Test	Acceptance Criteria	Analytical Procedure
Elemental Impurities ($\mu\text{g/g}$) ¹ (b) (4)	(b) (4)	ICP-MS (USP <233>, <232>; AD077 TST)
Microbial Bioburden Test Total Aerobic Count Total Yeasts & Mold Count Absence of objectionable organisms ⁴ (b) (4)	(b) (4)	Microbiological Examination (USP <61>, <62>; AD050 TST)
(b) (4)	(b) (4)	HPLC (AD073 TST)
(b) (4)	(b) (4)	GC (AD106 TST)
Residue on Ignition (% w/w) ^{1,5}	(b) (4)	(USP <281>; AD114 TST)

NMT = Not More Than; CFU = Colony Forming Units

- (b) (4)
- Structures and names of impurities are provided in Section 3.2.S.3.2.
- Total Impurities includes all impurities observed at or above (b) (4) % in the chromatographic purity test. (b) (4) is not included in the Total Impurities.
- Objectionable organisms: *Staphylococcus aureus*; *Pseudomonas aeruginosa*; *Bacillus subtilis*; *Candida albicans*; *Aspergillus brasiliensis*; *Escherichia coli*; *Salmonella enterica*; *Burkholderia cepacia*.
- As proposed in the Type B Pre-NDA CMC Meeting, IND 113064, Serial Number 0088, these tests will be (b) (4)

Section 3.2.S.4.5.

Drug Product:

Netarsudil ophthalmic solution 0.02% is a clear, sterile, preserved, isotonic solution at approximately pH 5. The formulation is packaged in a multi-dose LDPE bottles with (b) (4) LDPE dropper tips and white PP screw caps. In the NDA submission 2.5 mL fill size in 4 mL bottles for commercial and professional sample is proposed and (b) (4) fill size in 4 mL bottle may be used as a professional sample presentation in the future.

Drug product composition:

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FILING REVIEW

Table 1 **Composition and Components of Netarsudil Ophthalmic Solution 0.02%**

Component	Function	Netarsudil Concentration: 0.2 mg/mL	
		Quantity per mL (mg)	Quantity (% w/v)
Netarsudil mesylate	Active Ingredient	0.2 (b) (4)	0.02
Mannitol	(b) (4)	(b) (4)	(b) (4)
Boric acid	(b) (4)	(b) (4)	(b) (4)
Benzalkonium chloride	Preservative	(b) (4)	0.015
Sodium hydroxide ³	pH Adjuster	as needed	as needed
Water for Injection	(b) (4)	q.s.	q.s.
Total		1 mL	100%
(b) (4)			

Drug product specification:

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

Table 1 **Specifications for Netarsudil Ophthalmic Solution 0.02%**

Test	Acceptance Criteria
Description	Clear solution, free of visible particles
pH	(b) (4)
Osmolality (mOsm/kg)	(b) (4)
Identification of AR-13324 by UV ¹	UV Spectrum of sample is essentially the same as that of AR-13324 reference standard
Identification of AR-13324 by Retention Time ¹	The retention time of the AR-13324 peak corresponds to that of the AR-13324 reference standard
Assay: AR-13324 content (% LC)	(b) (4)
(b) (4)	(b) (4)
Any unspecified degradation product	(b) (4)
Total degradation products ³ (b) (4) (% w/w)	(b) (4)
Benzalkonium Chloride (% LC)	(b) (4)
Particulate Matter	NMT 50 particles/mL ≥10 μm NMT 5 particles/mL ≥25 μm NMT 2 particles/mL ≥50 μm
Sterility	Meets requirements of USP <71>
Antimicrobial Effectiveness Test ⁴	Meets Requirements of USP <51> for Category 1 product

UV = Ultraviolet detection LC = Label Claim NMT = Not More Than NLT = Not Less Than
(b) (4)

The proposed commercial scale is (b) (4). Twelve months stability data when stored at long term storage condition (5°C) and 6 months at accelerated condition (25°/40%RH) are provided for three registration batches with the scale of (b) (4). The stability studies were performed at upright and inverted orientations. The applicant performed leachable/ extractable, photostability and freeze-thaw study. The shelf-life of 24 months is proposed. The applicant also proposed the drug product can be stored at 2-25°C for up to 6 weeks once the bottle is opened. However, there is no in-use stability to support this statement.

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FILING REVIEW

Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
Sterility	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipment • Site 	<ul style="list-style-type: none"> • Non-sterile unit(s) 	4	5	4	80		H
Assay (API), stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	(b) (4)	3	2	2	6	(b) (4)	L
Assay (preservative)	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipment • Site 	<ul style="list-style-type: none"> • Lack of effectiveness through shelf-life 	1 (Release) 1 (Stability)	1	1	1	Preservative: BAC (b) (4)	L
Assay (b) (4)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters 	<ul style="list-style-type: none"> • Decrease in potency 					Not used	L

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FILING REVIEW

	<ul style="list-style-type: none"> Scale/equipment Site 							
Uniformity of Dose (Fill Volume/Deliverable volume)	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Insufficient dose 	4	3	1	12	(b) (4)	L
Osmolality	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Irritation Edema 	2	2	2		Osmolality testing is performed (DP specifications).	L
pH-	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Irritation Particulate formation due to delamination (with high pH) 	4	4	1	16	pH testing is performed (DP specifications).	L
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> Formulation Container closure Process parameters Scale/equipment Site 	<ul style="list-style-type: none"> Irritation Embolism 	3	5	4	60	Tested in DP specifications.	M
Leachable extractables	<ul style="list-style-type: none"> Formulation Container closure Process parameters 	<ul style="list-style-type: none"> Generation of impurities 	4	4	1	16	Test data provided	M

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

	<ul style="list-style-type: none"> • Scale/equipment • Site 							
Appearance (Color/turbidity)	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipment • Site 	3	3	1	9			L

Drug Product comments:

We remind you that if the cap color changes the change should be submitted as a Prior Approval Supplement including the results of extractables testing and a commitment to carry out leachables testing (IND 113064, minutes of the December 17, 2015 meeting, dated 1/14/16, see Question 10).

Please provide sample Certificates of Analysis showing that the water for injection meets USP standards for bacterial endotoxins.

With regard to the HPLC method for benzalkonium chloride we note that robustness is not demonstrated. In this respect it is noticeable (Report MVR-1945, page 10 of 39) that the [REDACTED] (b) (4) Please provide a robustness report or a justification for not conducting robustness testing.

In Report M-030-13 particulate matter is tested by [REDACTED] (b) (4) [REDACTED] (b) (4)

In the drug product specification please [REDACTED] (b) (4) or provide a justification for not doing so.

We note that the [REDACTED] (b) (4) Please comment.

We note your statement that after opening, the product may be kept at 2°-25 °C for up to 6 weeks. Please support this statement by conducting a one-time stability test for one batch of each presentation stored at 2-8°C for 24 months then at 25°C/40% RH for 6 weeks.

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

Facility comment:

With regard to your NDA 208254, please contact your proposed drug product manufacturer to confirm that the manufacturing lines proposed in your submission are currently ready for inspection. If the lines are not ready for inspection, please provide dates for when the lines will be ready.

The applicant responded on October 13, 2016, stating that:

The (b) (4) Certification of GMP Compliance dated 23 August 2016 included in the Rhopressa NDA states the (b) (4) facility complies with cGMP's in the procedures, facilities and controls used in the manufacture, process, packaging, labeling and testing of drug products. The (b) (4) facility was issued an NAI (No Action Indicated) rating for the FDA inspection conducted in (b) (4) per FDA's Inspections Classification Database. (b) (4) is currently manufacturing and distributing commercial product on (b) (4) which is used to produce the Rhopressa™ (netarsudil ophthalmic solution) 0.02% drug product.

Aerie conducted an audit of the (b) (4) facility in early (b) (4) and the results were reviewed by ex-FDA consultants. It is Aerie's opinion that the (b) (4) is ready for the PAI (Pre-Approval Inspection). We have not observed any issues with our product manufactured on (b) (4). We are aware, however, that there were observations cited during the (b) (4) PAI audit regarding their NDA for (b) (4) and will be ready for re-inspection of (b) (4) by the end (b) (4)



Chunchun
Zhang

Digitally signed by Chunchun Zhang
Date: 10/28/2016 12:25 06PM
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