

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208259Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Deputy Division Director Summary Review

Date	March 12, 2019
From	William M. Boyd, M.D. and Wiley A. Chambers, M.D.
Subject	Cross-Discipline Team Leader Review and Deputy Division Director Summary Review
NDA#	208259
Applicant	Aerie Pharmaceuticals, Inc.
Date of Submission	May 14, 2018
PDUFA Goal Date	March 14, 2019
Proprietary Name	Rocklatan
Established or Proper Name	Netarsudil and latanoprost ophthalmic solution
Dosage Form	Topical ophthalmic solution
Regulatory Action	Approval
Recommended Indication(s)	Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Recommended Dosing Regimen(s)	One drop in the affected eye(s) once daily in the evening

1. Benefit-Risk Assessment

Netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% (formerly PG324) is a fixed-dose combination (FDC) of 2 FDA-approved ocular hypotensive active components, netarsudil ophthalmic solution, 0.02% and latanoprost ophthalmic solution, 0.005%, and has been studied by Aerie Pharmaceuticals, Inc. (Aerie) as a once-daily treatment for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

The benefits of netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% in lowering intraocular pressure outweighs the risks to patients with open-angle glaucoma or ocular hypertension.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% dosed once daily in the affected eye(s) in the evening for lowering elevated IOP in patients with open-angle glaucoma or ocular hypertension. Elevated IOP is a major risk factor in the development of visual field loss in patients with open-angle glaucoma.

In Studies PG324-CS301 and PG324-CS302, the average IOP lowering effect of netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% was 1 to 3 mmHg greater than monotherapy with either netarsudil 0.02% or latanoprost 0.005% throughout 3 months. In Study -301, IOP reductions were maintained throughout 12 months.

The most common ocular adverse reaction observed in controlled clinical studies with netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% was conjunctival hyperemia which was reported in 59% of patients. Other common ocular adverse reactions reported were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

The potential benefits of netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% through lowering elevated IOP in patients with open-angle glaucoma or ocular hypertension outweigh the identified risks as demonstrated in the clinical studies submitted with this NDA application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated IOP.	Intraocular pressure establishes a direct measure of the efficacy of ocular hypotensive medications.
Current Treatment Options	There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, rho kinase inhibitors and prostaglandin analogues.	Different classes of products lower intraocular pressure by either decreasing aqueous production or increasing aqueous outflow.
Benefit	Additional reduction in IOP can be achieved by administering products from different classes of IOP reducing products.	The combination product demonstrated greater IOP reduction than either of the individual components given alone.
Risk	The adverse events previously identified in each of the individual components can be expected to occur in the combination product. No additional adverse reactions were identified in the clinical trials.	Labeling will identify the expected adverse reactions from each of components. Routine monitoring and reporting of all adverse events are expected to be adequate.

2. Background

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. It affects one person in 200 over the age of 40. It is the leading cause of irreversible blindness in the United States. One of the primary risk factors is elevated IOP. The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, rho kinase inhibitors and prostaglandin analogs.

Netarsudil ophthalmic solution, 0.2% was approved in the US in 2017 (Rhopressa). Latanoprost ophthalmic solution, 0.005% was approved in the US in 1996 (Xalatan).

Summary of Presubmission/Submission Regulatory Activity under IND 113064:

Type C Meeting to Discuss Clinical/Non-clinical plans	6/5/14
EOP2 Clinical/Non-clinical Meeting	3/24/15
EOP2 CMC Meeting	5/18/15
Request for Preliminary Advice-Breakthrough Therapy	5/24/16
Type C CMC meeting	5/10/17
Pre-NDA Meeting	8/18/17

This is a 505(b)(2) application. In order to bridge the nonclinical program of netarsudil and latanoprost ophthalmic solution to that of Rhopressa (data owned by Aerie) and Xalatan, Aerie conducted a comparative rabbit ocular tissue distribution study, comparative 3-day ocular tolerability studies in rabbits and monkeys, and a 3-month repeat-dose ocular toxicity study with netarsudil/latanoprost ophthalmic solution in rabbits. The data from these studies provides an adequate bridge to the nonclinical program of Rhopressa and Xalatan.

Netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% is not marketed in any other country.

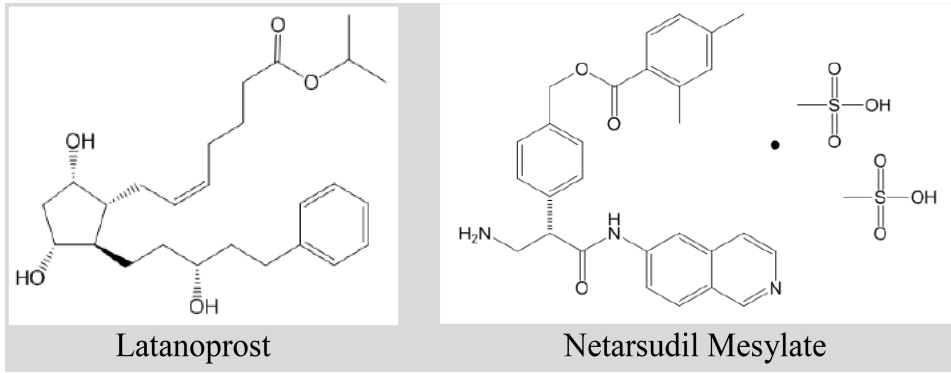
3. Product Quality

Summarized from the Quality Assessment reviews dated 2/6/2019 (IQA#1) and 2/27/2019 (IQA#2):

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

Drug Substance(s)

- **Latanoprost** = Isopropyl-(Z)-7 [(1R,2R,3R,5S) 3,5- dihydroxy-2-[(3R)- 3- hydroxy-5-phenylpentyl] cyclopentyl]-5-heptenoate
- **Netarsudil Mesylate** = Benzoic acid, 2,4-dimethyl-, [4-[(1S)-1-(aminomethyl)-2-(6-isoquinolinylamino)-2-oxoethyl]phenyl]methyl ester, methanesulfonate (1:2)



The latanoprost drug substance specifications provided in (b) (4) Type II DMF# (b) (4):

Test	Acceptance Criteria
Description*	(b) (4) yellow (b) (4) oil
Identification	
IR	Conform to reference IR spectrum
HPLC	Identical retention time as that of the reference standard
Specific Rotation (c=1 in acetonitrile, 20°C)	(b) (4)
Residue on Ignition / Sulphated Ash	NMT (b) (4) %
Water Content*	NMT (b) (4) %
Related Substances	
(b) (4)	NMT (b) (4) %
(b) (4)	NMT %
(b) (4)	NMT %
(b) (4)	NMT %
(b) (4)	NMT %
(b) (4)	NMT %
(b) (4)	NMT %
Residual Solvents (GC)	
(b) (4)	NMT (b) (4) ppm
(b) (4)	NMT ppm
(b) (4)	NMT ppm
(b) (4)	NMT ppm
(b) (4)	NMT (b) (4) ppm

Test	Acceptance Criteria
(b) (4)	NMT (b) (4) ppm
(b) (4)	NMT ppm
(b) (4)	NMT ppm
(b) (4)	NMT ppm
(b) (4)	NMT ppm
Limit of (b) (4) (GC)	Max. (b) (4) ppm
Assay (HPLC)*	(b) (4) % (b) (4)

*= (b) (4); NMT = Not more than; ppm = parts per millions. Source: Module 3.2.S.4.1 Specification

The proposed specification for netarsudil mesylate drug substance:

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)	NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT NMT NMT	HPLC (AD130 TST)
Chiral Impurity ((b) (4), % w/w)	NMT (b) (4)	HPLC (AD072 TST)
(b) (4) (% of theoretical value) ¹	(b) (4)	IC (AD121 TST)
(b) (4)	NMT (b) (4)	GC (AD082 TST)
Residual Solvents (ppm) ¹ (b) (4)	NMT (b) (4) NMT NMT NMT NMT	GC-HS (AD137 TST, (b) (4) TST ⁴) GC (AD142 TST ⁴)
Water Content (% w/w)	NMT (b) (4)	Karl Fischer (USP <921>; AD004 TST)
Elemental Impurities (µg/g) ¹ (b) (4)	NMT (b) (4) NMT NMT NMT NMT NMT	ICP-MS (USP <233>; AD077 TST)

Test	Acceptance Criteria	Analytical Procedure
Microbial Bioburden Test Total Aerobic Count Total Yeasts & Mold Count Absence of objectionable organisms ⁵	NMT ^{(b) (4)} CFU/ ^{(b) (4)} mg NMT ^{(b) (4)} CFU/ ^{(b) (4)} mg Absent	Microbiological Examination (USP <61>, <62>; AD050 TST)

NMT = Not More Than; CFU = Colony Forming Units

1. Tested only at release.
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. ^{(b) (4)}
5. Objectionable organisms: *Staphylococcus aureus*; *Pseudomonas aeruginosa*; *Bacillus subtilis*; *Candida albicans*; *Aspergillus brasiliensis*; *Escherichia coli*; *Salmonella enterica*; *Burkholderia cepacia*.

Source: Module 3.2.S.4.1 Specification

Drug Product

Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a clear, sterile, preserved, isotonic solution at approximately pH 5. The formulation is packaged as a multi-dose product and is preserved with benzalkonium chloride. The formulation is packaged in a ^{(b) (4)} multi-dose, low-density polyethylene (LDPE) bottle fitted with a white ^{(b) (4)} polyethylene ^{(b) (4)} dropper tip and a white polypropylene (PP) screw cap. The drug product is packaged in a ^{(b) (4)} 2.5 mL fill size (commercial and professional sample presentations).

The qualitative and quantitative composition is described below:

Composition and Components of Netarsudil 0.02% and Latanoprost 0.005% Ophthalmic Solution

Component	Function	Concentration	
		Quantity per mL (mg)	Quantity (% w/v)
Netarsudil mesylate	Active Ingredient	0.2 (0.2849) ¹	0.02
Latanoprost	Active Ingredient	0.05 ^{(b) (4)}	0.005
Mannitol	^{(b) (4)}		
Boric acid			
Benzalkonium chloride			
Sodium hydroxide ⁴			
Water for Injection			
Total			1 mL

¹ Netarsudil mesylate concentration is expressed in the formula as the free base; the amount required represents the amount being added as the dimesylate salt. ^{(b) (4)}

^{(b) (4)} (0.2849 mg/mL).



Source: Module 3.2.P.1 Description and Composition of the Drug Product

The proposed release and stability commercial specifications for Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% are provided below:

Specifications for Netarsudil 0.02% and Latanoprost 0.005% Ophthalmic Solution

Test	Acceptance Criteria
Description	Clear solution, free of visible particles
pH	(b) (4)
Osmolality (mOsm/kg)	(b) (4)
Identification of Netarsudil by UV ¹	UV Spectrum of sample is essentially the same as that of the netarsudil reference standard
Identification of Netarsudil by Retention Time ¹	The retention time of the main peak in the sample corresponds to that of the netarsudil reference standard
Identification of Latanoprost by UV ¹	UV Spectrum of sample is essentially the same as that of the latanoprost reference standard
Identification of Latanoprost by Retention Time ¹	The retention time of the main peak in the sample corresponds to that of the latanoprost reference standard
Assay: Netarsudil content (% LC)	(b) (4)
Assay: Latanoprost content (% LC)	(b) (4)
Netarsudil specified identified degradation products (% w/w)	
(b) (4)	NMT (b) (4)
(b) (4)	NMT
(b) (4)	NMT
(b) (4)	NMT
Netarsudil specified unidentified degradation products (% w/w) ²	NMT (b) (4)
(b) (4)	(b) (4)
Any netarsudil unspecified degradation product	NMT (b) (4)
Total netarsudil degradation products ³	NMT
Chiral Impurity: (b) (4) content (% w/w)	NMT
Latanoprost specified identified degradation products (% w/w)	
(b) (4)	NMT
(b) (4)	NMT
(b) (4)	NMT
(b) (4)	NMT

Latanoprost specified unidentified degradation products (% w/w) ⁴ (b) (4)	NMT (b) (4)
Any latanoprost unspecified degradation product	NMT (b) (4)
Total latanoprost degradation products (b) (4) (% LC)	NMT (b) (4) (b) (4)
Particulate Matter	Meets requirement of USP <789> NMT (b) (4) particles/mL (b) (4) μm NM (b) (4) particles/mL (b) (4) μm NM (b) (4) particles/mL (b) (4) μm
Sterility	Meets requirements of USP <71>

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

1. Tested only at release.
2. The degradation products are tracked by relative retention time (RRT) and reported as % w/w with respect to the netarsudil peak.
3. The Total Degradation Products does not include the level of (b) (4).
4. The degradation products are tracked by relative retention time (RRT) and reported as % w/w with respect to the latanoprost peak.

Source: Module 3.2.P.5.1 Specifications

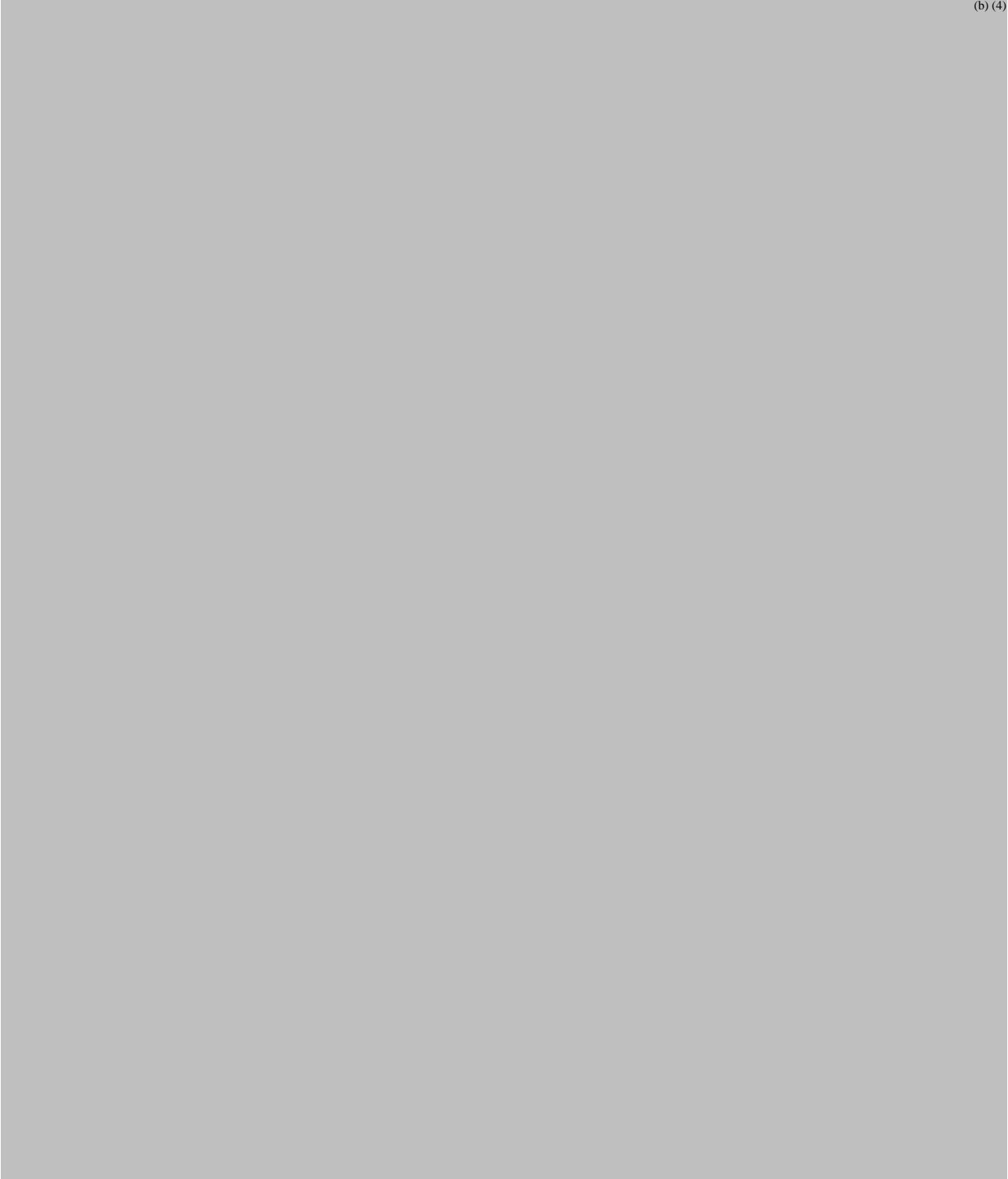
Container Closure

The container closure system for the drug product is comprised of a sterilized ophthalmic dropper bottle (4 mL, (b) (4) low density polyethylene (LDPE) bottle) with a (b) (4) dropper tip and (b) (4) cap.

The primary packaging components (bottle, tip and cap) for netarsudil 0.02% and latanoprost 0.005% ophthalmic solution (b) (4)

Description of Packaging Components

(b) (4)



Source: Module 3.2.P.7 Container Closure System

Inspections

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)	(b) (4)	Drug product manufacturer (SNI) Performs release testing for raw material/excipients, and packaging components; performs drug product release and stability testing	High	Originally it was withheld due to the OAI classification. Based on the (b) (4) follow-up inspection, the OAI classification was downgraded to NAI on 2/22/2019. Thus, it is acceptable.
		Alternate site for drug product release and stability testing	High	Acceptable
		(b) (4) the container-closure system components		No further evaluation

Drug substance, drug product, biopharmaceutics, manufacturing process and quality micro reviewers have recommended approval of NDA 208259 as documented in IQA #1. The drug product manufacturing facility, (b) (4) is classified as NAI based on the recent inspection ending (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.

4. Nonclinical Pharmacology/Toxicology

Summarized from the Pharmacology/Toxicology review in DARRTS dated 1/23/2019:

In order to bridge the nonclinical program of netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% to that of Rhopressa and Xalatan, Aerie conducted a comparative rabbit ocular tissue distribution study, comparative 3-day ocular tolerability studies in rabbits and monkeys, and a 3-month repeat-dose ocular toxicity study in rabbits. For nonclinical information pertaining to latanoprost, Aerie relied on the Agency’s findings of safety and effectiveness for Xalatan, specifically, the currently approved Xalatan prescribing information (approved April 10, 2017).

The ocular tissue distribution study in rabbits following a single topical ocular administration of radiolabeled FDC netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% (PG324 Ophthalmic Solution) showed no toxicologically relevant differences in ocular tissue distribution, blood and plasma PK profiles compared to each active component of the combination alone.

In 3-day comparable ocular tolerability studies, trace and transient conjunctival hyperemia was observed in rabbits treated with the FDC formulation, as well as rabbits treated with the single-agent formulations, i.e., Xalatan and netarsudil ophthalmic solution, 0.02%. The conjunctival hyperemia could be related to irritation and/or a pharmacological effect (i.e., dilatation of blood vessels) of both netarsudil and latanoprost.

In monkeys, no signs of ocular hyperemia or irritation were observed with any formulation. However, the FDC formulation produced substantially larger IOP reductions (the expected pharmacological activity) compared to Xalatan. The FDC formulation also showed increased efficacy compared to netarsudil ophthalmic solution, 0.02%. at later timepoints (after the 3rd daily dose on Day 3).

In the 3-month ocular toxicity study, findings in rabbits treated with netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% QD or BID were limited to mild to moderate redness of the eye (conjunctiva and/or sclera), which was noted sporadically, and transient decreases in IOP. These findings have been previously observed in ocular toxicity studies conducted with netarsudil (NDA 208254). The NOAEL was the high dose, netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% BID, providing an exposure margin of 2X the intended clinical dose regimen (i.e., QD).

The data from these studies provides an adequate bridge to the nonclinical program of Rhopressa and Xalatan. The nonclinical data presented in this NDA provides adequate safety support for the intended dosing regimen of netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% once daily for the indication of reduction of IOP.

5. Clinical Pharmacology

Clinical Pharmacology did not conduct a review for this combination product. The new drug application for Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% contains no new PK information and/or studies that were conducted using this combination. No further PK evaluation is needed for this product. The labeling language for Rocklatan proposed in Section 12.3 for PK contains the same wording as for the approved labeling for netarsudil ophthalmic solution (Rhopressa) and latanoprost ophthalmic solution (Xalatan).

6. Clinical Microbiology

Not applicable. Product is not an anti-infective.

7. Clinical/Statistical- Efficacy

From the Medical Officer review in DARRTS dated 3/5/2019:

Table of Studies/Clinical Trials

Study Name	Study Design	Test product	Number of Subjects	Duration of Treatment	Study Status
PG324-CS201 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled study	Netarsudil 0.01% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil ophthalmic solution 0.02% 1 gtt OU QD PM Latanoprost ophthalmic solution 0.005% 1 gtt OU QD PM	298	28 days	Complete
PG324-CS301 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled parallel study	Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil ophthalmic solution 0.02% 1 gtt OU QD PM Latanoprost ophthalmic solution 0.005% 1 gtt OU QD PM	718	12 months (3 months efficacy, 12 months safety) with optional 2 months Observation	Complete
PG324-CS302 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled parallel study	Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil ophthalmic solution 0.02% 1 gtt OU QD PM Latanoprost ophthalmic solution 0.005% 1 gtt OU QD PM	750	3 months	Complete
AR-13324-CS206 Effect on trabecular outflow facility; ocular and systemic safety	Double-masked, Vehicle controlled, Paired comparison	Netarsudil ophthalmic solution 0.02% 1 gtt OU QD AM Netarsudil ophthalmic solution vehicle 1 gtt OU AM	20	7 days	Ongoing
PG324-CS303 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled parallel study	Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Ganfort® (bimatoprost 0.03%/timolol maleate 0.5% ophthalmic solution) 1 gtt OU QD PM	472	6 months (3 months efficacy; 6 months safety)	Ongoing

The two studies which provide the main support for safety and efficacy were: Protocol PG324-CS301 which enrolled 718 subjects for the twelve-month treatment period at 58 sites in the U.S and Protocol PG324-CS302 which enrolled 750 subjects for the three-month treatment period at 60 sites in the U.S.

Study PG324-CS301: Mean Eye IOP (mmHg) By Visit (ITT With LOCF)

Day and Time	Mean IOP Netar/Lat N=238	Mean IOP Netar N=244	Mean IOP Lat N=236	Mean Diff From Net	95% CI P-value	Mean Diff From Lat	95% CI P-value
Day 1							
08:00	24.84	24.81	24.59	0.03	(-0.57, 0.62) 0.92	0.25	(-0.31, 0.81) 0.39
10:00	23.72	23.45	23.43	0.27	(-0.36, 0.91) 0.40	0.29	(-0.34, 0.92) 0.37
16:00	22.59	22.63	22.43	-0.03	(-0.69, 0.62) 0.92	0.16	(-0.47, 0.79) 0.61
Day 15							
08:00	15.92	18.75	17.80	-2.83	(-3.56, -2.10) <0.01	-1.88	(-2.54, -1.21) <0.01
10:00	15.15	18.00	17.43	-2.86	(-3.58, -2.13) <0.01	-2.29	(-2.94, -1.63) <0.01
16:00	15.07	17.41	17.20	-2.34	(-2.99, -1.69) <0.01	-2.13	(-2.73, -1.52) <0.01
Day 43							
08:00	16.27	19.18	17.69	-2.91	(-3.66, -1.93) <0.01	-1.42	(-2.31, -1.03) <0.01
10:00	15.26	18.25	17.24	-2.65	(-3.37, -1.93) <0.01	-1.64	(-2.28, -1.00) <0.01
16:00	15.63	17.82	17.10	-2.19	(-2.86, -1.92) <0.01	-1.48	(-2.11, -0.85) <0.01
Day 90							
08:00	16.50	19.49	17.62	-2.99	(-3.78, -2.19) <0.01	-1.11	(-1.78, -0.45) <0.01
10:00	15.55	18.56	17.00	-3.01	(-3.75, -2.26) <0.01	-1.48	(-2.11, -0.85) <0.01
16:00	15.66	17.76	16.83	-2.11	(-2.79, -1.43) <0.01	-1.18	(-1.80, -0.55) <0.01

The primary endpoint with actual mean IOP (without ANCOVA modeling) and ITT with LOCF baseline mean IOP of the three treatment groups is similar. The 95% confidence intervals cross zero at all time points measured at baseline.

The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured at Day 15, Day 43, and Day 90. In addition, the mean difference between the fixed combination and netarsudil is statistically significant at all time points at Day 15, Day 43, and Day 90.

Study PG324-CS302: Mean Eye IOP (mmHg) By Visit (ITT With LOCF)

Day and Time	Mean IOP Netar/Lat N=245	Mean IOP Netar N=255	Mean IOP Lat N=250	Mean Diff from Netar	95% CI P-value	Mean Diff from Lat	95% CI P-value
Day 1							
08:00	24.69	24.66	24.75	0.04	(-0.54, 0.61) 0.90	-0.05	(-0.64, 0.54) 0.86
10:00	23.33	23.40	23.23	-0.07	(-0.68, 0.54) 0.82	0.11	(-0.49, 0.70) 0.72
16:00	22.37	22.76	22.59	-0.39	(-1.01, 0.23) 0.22	-0.22	(-0.83, 0.39) 0.48
Day 15							
08:00	16.27	19.42	18.18	-3.15	(-3.85, -2.45) <0.01	-1.91	(-2.54, -1.29) <0.01
10:00	15.55	18.12	17.65	-2.57	(-3.24, -1.91) <0.01	-2.11	(-2.71, -1.50) <0.01
16:00	15.41	17.69	17.16	-2.28	(-2.91, -1.65) <0.01	-1.74	(-2.33, -1.15) <0.01
Day 43							
08:00	16.64	19.63	17.96	-2.98	(-3.72, -2.25) <0.01	-1.32	(-1.99, -0.65) <0.01
10:00	15.77	18.50	17.39	-2.73	(-3.41, -2.05) <0.01	-1.73	(-2.39, -1.07) <0.01
16:00	15.65	18.05	17.16	-2.40	(-3.07, -1.73) <0.01	-1.50	(-1.93, -0.64) <0.01
Day 90							
08:00	16.69	20.08	18.05	-3.39	(-4.15, -2.63) <0.01	-1.36	(-2.02, -0.71) <0.01
10:00	15.84	18.66	17.53	-2.82	(-3.51, -2.13) <0.01	-1.69	(-2.32, -1.06) <0.01
16:00	15.74	18.32	17.16	-2.58	(-3.24, -1.92) <0.01	-1.42	(-2.02, -0.81) <0.01

The primary endpoint with actual mean IOP (without ANCOVA modeling) and ITT with LOCF baseline mean IOP of the three treatment groups is similar. The 95% confidence intervals cross zero at all time points measured at baseline.

The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured at Day 15, Day 43, and Day 90. In addition, the mean difference between the fixed combination and netarsudil is statistically significant at all time points at Day 15, Day 43, and Day 90.

Summary of Efficacy:

Studies PG324-CS301 and PG324-CS302, mean IOP measured at multiple time points, achieved their primary endpoint. The average IOP lowering effect of netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% was 1 to 3 mmHg greater than monotherapy with either netarsudil 0.02% or latanoprost 0.005% throughout 3 months.

8. Safety

From the Medical Officer review in DARRTS dated 3/5/2019:

Extent of Exposure

Study PG324-CS301: Exposure to Study Medication by Treatment Group (Safety Population)

	Netarsudil/Latanoprost QD N=244	Netarsudil QD N=243	Latanoprost QD N=237
Mean Days of Exposure	276	266	330

Study PG324-CS302: Exposure to Study Medication by Treatment Group (Safety Population)

	Netarsudil/Latanoprost QD N=244	Netarsudil QD N=255	Latanoprost QD N=251
Mean Days of Exposure	85	85	88

Deaths

Study PG324-CS301: One death was reported during the study. Subject (b) (6) died presumably from atherosclerotic and hypertensive cardiovascular disease after 252 days on treatment (netarsudil).

Study PG324-CS302: One death was reported during the study. Subject (b) (6) suffered a fatal cardiac arrest after 47 days on treatment (netarsudil).

Study PG324-CS301: There were 32 SAEs reported from 25 subjects. Six SAEs (5 subjects) were in the netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% treatment group and 12 SAEs (10 subjects) were in the netarsudil group. The remaining 14 SAEs (10 subjects) were reported in the latanoprost group. All SAEs reported during the treatment period were non-ocular SAEs.

Study PG324-CS302: A total of 13 subjects reported a total of 15 SAEs. Two of the subjects reporting 3 SAEs were in the netarsudil and latanoprost ophthalmic solution, 0.02%/0.005%, and a total of 6 subjects in the netarsudil group reported 7 SAEs; the remaining 5 SAEs were reported by 5 subjects in the latanoprost group. One of the 15 SAEs reported was coded to an eye disorder, a retinal detachment in a subject treated with latanoprost.

Common Ocular Adverse Events

**Studies -301 and -302: Ocular TEAEs Occurring at an Incidence of $\geq 1\%$
 (Safety Population)**

	Netarsudil 0.02% /Latanoprost 0.005%		Netarsudil 0.02%		Latanoprost 0.005%	
	CS301	CS302	CS301	CS302	CS301	CS302
	N=238	N=244	N=243	N=255	N=237	N=251
Any TEAE	197	171	190	161	128	109
Eye disorders						
Conjunctival hyperemia	150	133	125	109	52	56
Conjunctival hemorrhage	31	21	44	28	3	2
Corneal verticillata	42	32	33	25	0	0
Eye pruritis	27	10	22	1	3	2
Punctate keratitis	12	5	18	9	10	4
Lacrimation increased	17	8	20	8	1	0
Visual acuity reduced	13	12	13	8	6	3
Vision blurred	11	12	15	8	3	4
Blepharitis	15	4	8	6	5	1
Eye irritation	11	4	7	6	3	1
Erythema of eyelid	10	8	9	5	1	3
Conjunctivitis allergic	8	2	11	3	0	0
Conjunctival edema	9	3	7	3	1	1
Eyelid edema	6	8	9	6	2	3
Dry eye	6	1	3	3	6	3
Meibomian gland dysfunction	5		5		2	
Eye pain	4	3	6	5	0	4
FBS in eyes	4	7	5	1	1	2
Cataract	1		6		2	
Chalazion	5		3		0	
Conjunctival disorder	3		3		2	
Eyelid pruritis	5		3		0	
Miosis	2		2		3	
Vitreous detachment	2		2		3	
Photophobia	4		1		1	
Corneal deposits	5		0		0	
Eyelid margin crusting	4	3	1	3	0	0
Corneal opacity	1		3		0	
General disorders						
Instillation site pain	55	42	60	23	18	15
Instillation site discomfort	10	15	7	16	3	2
Instillation site erythema	10	10	5	6	1	4
Instillation site FBS	0		6		3	
Peripheral swelling	0		0		3	
Infections						
Conjunctivitis	1		4		1	
Investigations						
Vital dye staining cornea present	8	10	7	14	3	7
IOP increased	0		4		1	

	Netarsudil 0.02% /Latanoprost 0.005%		Netarsudil 0.02%		Latanoprost 0.005%	
	CS301	CS302	CS301	CS302	CS301	CS302
	N=238	N=244	N=243	N=255	N=237	N=251
Nervous system disorders						
VF defect	5		3		1	
Skin disorders						
Dermatitis contact	7		3		0	

The Agency sent an IR to the Applicant stating that corneal disorders in Study 302 should be specified as they were in Study 301. The Applicant responded to the IR SDN-17 (1/31/19) stating: Table 16 in both PG324-CS301 and PG324-CS302 CSRs are similar in design. The main reason for the apparent difference is that in Study PG324-CS302 the 2 Verbatim Terms “distortion of specular microscopy corneal endothelial cell morphology” and “endothelial cell pleomorphism” were mapped to the Preferred Term (PT) “corneal disorder”, whereas in Study PG324-301 the Verbatim Term “corneal anterior basement membrane changes” was mapped to the PT “corneal disorder”. However, there was only 1 subject in the latanoprost arm with “corneal anterior basement membrane changes”, which is not shown in Table 16 because of the 1% incidence cut-off. There were no treatment-emergent adverse events (TEAEs) regarding endothelial cell morphology or pleomorphism in Study PG324-CS301 and no basement membrane changes in Study PG324-CS302. The PT “corneal disorder” was used in both studies, because it was most relevant for mapping the endothelial cell morphology/pleomorphism and basement membrane changes using MedDRA Version 19.0. Furthermore, in Study PG324-302 there were 3 subjects with TEAEs mapped to the PT “corneal opacity”, 1 subject in the PG324 arm and 2 subjects in the netarsudil arm, which are also below the 1% incidence cut-off used in Table 16. This response was acceptable. Only Study -302 evaluated endothelial cell count.

Summary of Safety:

The safety database contained in this submission (including Studies PG324-CS301 and PG324-CS302) establishes the relative netarsudil and latanoprost ophthalmic solution, 0.02%/0.005%, dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

In the May 5, 2015, End of Phase 2 meeting, the Sponsor stated that the Phase 3 clinical protocols for netarsudil and latanoprost ophthalmic solution, 0.02%/0.005% would include subjects 18 years of age and older, with the acknowledgement that the risks associated with prostaglandin analogues (i.e., permanent darkening of iris, skin discoloration and loss of orbital fat) may not be appropriate for pediatric patients. Therefore, the Sponsor proposed to seek a waiver in the pediatric study plan (PSP) for inclusion of subjects 0-17 years of age in the Phase 3 studies. On June 10, 2015, the Sponsor submitted a Pediatric Study Plan (PSP) which described plans to

request a full waiver of pediatric studies. In an August 28, 2015, Advice Letter, the Agency agreed to the iPSP.

This application triggers PREA as a new active ingredient and went to the Pediatric Review Committee (PeRC) on October 10, 2018. PeC noted that Aerie was requesting a full waiver of pediatric studies because studies would be impossible or highly impracticable. The Division stated that the labeling will reflect the safety concerns with pigmentation. The PeRC agreed with the full waiver as outlined in the Agreed iPSP.

11. Other Relevant Regulatory Issues

Biostatistics

Per the Biostatistics review dated 2/8/2019:

Studies 301 and 302 Mean IOP and Mean IOP Change from Baseline by Visit and Time
 (Based on Observed Data)

	PG324			Netarsudil			Latanoprost			PG324 vs. Netarsudil Differences (95% CI*) ¹	PG324 vs. Latanoprost Differences (95% CI*) ¹
Study 301	N	IOP	Ch*	N	IOP	Ch*	N	IOP	Ch*		
Baseline											
8am	238	24.8	n/a	244	24.8	n/a	236	24.6	n/a	0.0 (-0.6, 0.6)	0.3 (-0.3, 0.8)
10am	238	23.7	n/a	244	23.5	n/a	236	23.4	n/a	0.3 (-0.4, 0.9)	0.3 (-0.3, 0.9)
4pm	238	22.6	n/a	244	22.6	n/a	236	22.4	n/a	-0.0 (-0.7, 0.6)	0.2 (-0.5, 0.8)
Day 15											
8am	231	15.6	-9.1	241	18.6	-6.1	234	17.8	-6.9	-3.0 (-3.6, -2.5)	-2.3 (-2.8, -1.7)
10am	232	14.9	-8.7	236	17.9	-5.7	232	17.4	-6.1	-3.0 (-3.6, -2.4)	-2.6 (-3.2, -2.0)
4pm	231	14.8	-7.7	237	17.2	-5.3	231	17.2	-5.4	-2.4 (-3.0, -1.9)	-2.3 (-2.9, -1.8)
Day 43											
8am	221	16.0	-8.9	227	19.1	-5.6	226	17.7	-7.1	-3.2 (-3.8, -2.6)	-1.7 (-2.4, -1.1)
10am	217	15.2	-8.3	223	18.1	-5.5	225	17.1	-6.5	-2.8 (-3.5, -2.3)	-1.9 (-2.5, -1.2)
4pm	216	15.3	-7.2	223	17.6	-4.9	225	17.0	-5.5	-2.3 (-2.8, -1.7)	-1.7 (-2.2, -1.1)
Day 90											
8am	204	16.1	-8.6	205	19.3	-5.5	223	17.6	-7.2	-3.1 (-3.8, -2.5)	-1.5 (-2.1, -0.9)
10am	200	15.2	-8.3	200	18.4	-5.2	223	16.9	-6.7	-3.2 (-3.8, -2.5)	-1.7 (-2.3, -1.1)
4pm	200	15.4	-7.1	198	17.4	-5.1	223	16.7	-5.9	-2.0 (-2.6, -1.4)	-1.3 (-1.9, -0.7)
Study 302	N	IOP	Ch*	N	IOP	Ch*	N	IOP	Ch*		
Baseline											
8am	245	24.7	n/a	255	24.7	n/a	250	24.8	n/a	0.0 (-0.5, 0.6)	-0.1 (-0.6, 0.5)
10am	245	23.3	n/a	255	23.4	n/a	250	23.2	n/a	-0.1 (-0.7, 0.5)	0.1 (-0.5, 0.7)
4pm	245	22.4	n/a	255	22.8	n/a	250	22.6	n/a	-0.4 (-1.0, 0.2)	-0.2 (-0.8, 0.4)
Day 15											
8am	238	16.1	-8.7	252	19.4	-5.3	246	18.1	-6.6	-3.4 (-3.9, -2.8)	-2.0 (-2.6, -1.5)
10am	236	15.3	-8.1	249	18.0	-5.4	247	17.7	-5.7	-2.7 (-3.2, -2.2)	-2.4 (-2.9, -1.9)
4pm	235	15.2	-7.3	248	17.5	-5.1	247	17.1	-5.5	-2.2 (-2.8, -1.7)	-1.9 (-2.4, -1.3)
Day 43											
8am	234	16.4	-8.3	248	19.6	-5.2	242	17.9	-6.8	-3.2 (-3.8, -2.6)	-1.5 (-2.1, -0.9)

10am	233	15.5	-7.8	247	18.4	-5.0	242	17.4	-6.0	-2.9 (-3.4, -2.3)	-1.9 (-2.4, -1.3)
4pm	232	15.5	-7.1	247	17.9	-4.7	241	17.1	-5.5	-2.3 (-2.9, -1.8)	-1.6 (-2.1, -1.0)
Day 90											
8am	223	16.4	-8.3	231	20.0	-4.7	236	17.9	-6.8	-3.6 (-4.2, -3.0)	-1.5 (-2.2, -0.9)
10am	222	15.6	-7.8	228	18.4	-5.0	236	17.5	-5.8	-2.8 (-3.4, -2.3)	-2.0 (-2.5, -1.4)
4pm	221	15.6	-7.0	228	18.0	-4.6	236	17.1	-5.5	-2.4 (-2.9, -1.9)	-1.5 (-2.1, -1.0)

Ch* = Change in IOP from baseline. CI = Confidence Interval.

¹ The treatment differences and two-sided CIs for comparing PG324 vs. each of its active component are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.2 of Study 301 Report and Table 14.2.1.1.2 of Study 302 Report for IOP; Statistical Reviewer’s analyses for the mean IOP change from baseline.

Both studies demonstrated statistically significantly higher mean IOP reductions in the PG324 group compared with its two components at the nine post-baseline time points. As shown in Table 2, in Study 301, IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.1 to 9.1 mmHg in the PG324 group, 4.9 to 6.1 mmHg in the netarsudil group, and 5.4 to 6.9 mmHg in the latanoprost group. The treatment differences between PG324 and netarsudil groups ranged from -3.2 mmHg to -2.0 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.6 mmHg to -1.3 mmHg. In Study 302, IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.0 to 8.7 mmHg in the PG324 group, 4.6 to 5.4 mmHg in the netarsudil group, and 5.5 to 6.8 mmHg in the latanoprost group. The treatment differences between PG324 and netarsudil groups ranged from -3.6 mmHg to -2.2 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.4 to -1.5 mmHg.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

Investigator (b) (6) (Study -301) held significant equity interest defined as > \$50,000.00. (b) (6) enrolled (b) (6)

OSI

A routine Office of Scientific Investigations (OSI) audit was requested. Per the OSI review dated 1/9/2019:

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).

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.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Rocklatan, and granted conditional acceptance on 7/23/2018.

DMEPA completed a labeling review of the 5/14/2018 package insert and 7/25/2018 carton/container labeling on 7/31/2018. DMEPA recommended:

- (b) (4)
- Addition of a linear barcode to the trade container label (per 21 CFR 201.25).
- Increased size of product strength on principal display panel.

OPDP

The Office of Prescription Drug Promotion (OPDP) completed a review of the draft, substantially complete USPI and carton/container labeling on 2/14/2019.

12. Postmarketing Recommendations

A risk management plan is not necessary given the known risks of these classes of products.

PMC

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with Xalatan (latanoprost ophthalmic solution) 0.005%. Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a fixed dose combination product containing latanoprost ophthalmic solution, 0.005%. Specific drug interaction studies have not been conducted with Rocklatan, and the currently proposed Rocklatan labeling states in Section 7,

“Although specific drug interaction studies have not been conducted with ROCKLATAN, *in vitro* studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost ophthalmic solution 0.005%.”

The goal of the requested PMC *in vitro* study is to determine if precipitation occurs when eye drops containing thimerosal are mixed with the fixed dose combination, Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%.

In their March 7, 2019, submission, the applicant agreed to the PMC and the associated timeline noted below. The following statements should be included in the approval letter for the application:

3584-1 To conduct an *in vitro* study to determine if the precipitation occurs when eye drops containing thimerosal are mixed with Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%.

The timetable you submitted on March 7, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2019
Study/Trial Completion: 12/2019
Final Report Submission: 03/2020

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 113064 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

13. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Sec 6.1 Study endpoints
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

14. Labeling

Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% will be approved for the for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension based on adequate and well controlled clinical trials with the labeling below (submitted March 8, 2019).

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

WILLIAM M BOYD
03/12/2019 07:33:29 AM

WILEY A CHAMBERS
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