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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	208259
Supporting document/s:	1
Applicant's letter date:	5-14-2018
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Product:	Rocklatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%
Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant:	Aerie Pharmaceuticals, Inc
Review Division:	Transplant and Ophthalmology Products
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1 Executive Summary

1.1 Introduction

Netarsudil/latanoprost ophthalmic solution (Rocklatan) is a fixed-dose combination (FDC) product containing netarsudil 0.02% and latanoprost 0.005% active ingredients in the same concentrations as the currently approved single-agent ophthalmic solutions:

- Rhopressa® (netarsudil ophthalmic solution) 0.02% (Aerie's NDA 208254; approved 12/18/2017)
- Xalatan® (latanoprost ophthalmic solution) 0.005% (Pfizer's NDA 020597; approved 06/05/1996)

Netarsudil is a Rho kinase inhibitor; latanoprost is a PGF2α analog. The intended indication for netarsudil/latanoprost ophthalmic solution (i.e., reduction of intraocular pressure [IOP] in patients with open-angle glaucoma or ocular hypertension), and dosing regimen (i.e., one drop in the affected eye[s] once daily in the evening) are the same as those approved for the single-agent ophthalmic solutions.

This NDA have been filed as a 505(b)(2) application. In order to bridge the nonclinical program of netarsudil/latanoprost ophthalmic solution 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). Articles from the published literature were referenced to support the molecular mechanism of Rho-kinase inhibitors in the reduction of IOP and the mechanism for dilatation of conjunctival blood vessels, producing hyperemia.

1.2 Brief Discussion of Nonclinical Findings

The ocular tissue distribution study in rabbits following a single topical ocular administration of radiolabeled FDC netarsudil 0.02%/latanoprost 0.005% ophthalmic solution (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 (0.02% AR-13324 Ophthalmic Solution). 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

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expected pharmacological activity) compared to Xalatan®. The FDC formulation also showed increased efficacy compared to 0.02% netarsudil at later timepoints (after the 3rd daily dose on Day 3).

In the 3-month ocular toxicity study, findings in rabbits treated with netarsudil 0.02%/latanoprost 0.005% ophthalmic solution 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 0.02%/latanoprost 0.005% BID, providing an exposure margin of 2X the intended clinical dose regimen (i.e., QD).

Therefore, 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 0.02%/latanoprost 0.005% ophthalmic solution once daily for the indication of reduction of IOP.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Aerie's proposed language	FDA reviewer recommendations
8.1 Pregnancy Risk Summary (b) (4) [redacted] however, systemic exposure to netarsudil from ocular administration is low [*see Clinical Pharmacology (12.3)*]. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures [*see Data*]. (b) (4) [redacted] (b) (4) [redacted]	**8.1 Pregnancy** Risk Summary There are no adequate and well-controlled studies of ROCKLATAN ophthalmic solution or its pharmacologically active ingredients (netarsudil and latanoprost) in pregnant women to inform any drug-associated risk. However, systemic exposure to netarsudil from ocular administration is low [*see Clinical Pharmacology (12.3)*]. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures [*see Data*]. Reproduction studies of latanoprost showed embryofetal lethality in rabbits. No embryofetal

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	lethality was observed at a dose approximately 15 times higher than the RHOD. ROCKLATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
<u>Data</u> *Animal Data* Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}). Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).	<u>Data</u> *Animal Data* No edits to netarsudil proposed language
(b) (4)	Reproduction studies have been performed with latanoprost in rats and rabbits. In 4 of 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD.

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8.2 Lactation Risk Summary There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. (b) (4) [redacted] The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ROCKLATAN and any potential adverse effects on the breast-fed child from netarsudil and latanoprost.	**8.2 Lactation** Risk Summary There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low (b) (4) [redacted] and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ROCKLATAN and any potential adverse effects on the breast-fed child from ROCKLATAN.
12.1 Mechanism of Action ROCKLATAN is comprised of two components: netarsudil (b) (4) [redacted] and latanoprost (b) (4) [redacted]. Each of these two components decreases elevated IOP. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and glaucomatous visual field loss. ROCKLATAN is believed to reduce IOP by increasing the outflow of aqueous humor (b) (4) [redacted]	**12.1 Mechanism of Action** No edits (b) (4) [redacted]
13. Nonclinical Toxicology **Carcinogenesis, Mutagenesis, Impairment of Fertility** Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. (b) (4) [redacted] Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the RHOD) for up to 20 and 24 months, respectively. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse	**13. Nonclinical Toxicology** **Carcinogenesis, Mutagenesis, Impairment of Fertility** *Carcinogenesis* Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the RHOD) for up to 20 and 24 months, respectively. *Mutagenesis*

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micronucleus tests. Chromosome aberrations were observed *in vitro* with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.	Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed *in vitro* with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. *Impairment of Fertility* Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed. Latanoprost has not been found to have effects on male or female fertility in animal studies.

2 Drug Information

2.1 Drug

The test article is a fixed combination product of netarsudil and latanoprost. The code name PG324 was used during development for the combination product netarsudil 0.02% and latanoprost 0.005% ophthalmic solution.

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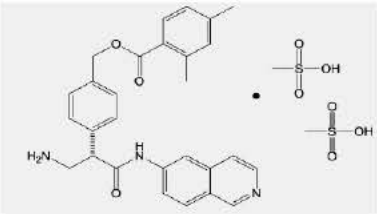
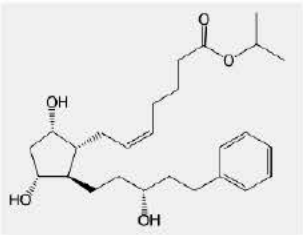
	Netarsudil mesylate	**Latanoprost**
CAS Registry Number (Optional)	1422144-42-0	130209-82-4
Generic Name	Netarsudil mesylate	Latanoprost
Code Name	AR-13324	
Chemical Name	Benzoic acid, 2,4-dimethyl-, [4-[(1S)-1-(aminomethyl)-2-(6 isoquinolinyl-amino)-2-oxoethyl]phenyl]methyl ester, methanesulfonate (1:2) (S)-4-(3-amino-1-(isoquinolin-6-yl-amino)-1-oxopropan-2-yl)benzyl 2,4-dimethylbenzoate dimesylate	Isopropyl-(Z)-7 [(1R,2R,3R,5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl] cyclopentyl]-5-heptenoate
Molecular Formula/Molecular Weight	Dimesylate salt: $C_{30}H_{35}N_3O_9S_2$/645.74 g/mol Free base: $C_{28}H_{27}N_3O_3$/453.53 g/mol	$C_{26}H_{40}O_5$/432.6 g/mol
Structure	 Netarsudil mesylate is a chiral molecule, [redacted] (b) (4) as a single enantiomer. (b) (4) [redacted]	
Pharmacologic Class	Rho kinase inhibitor	PGF2α analog

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 113064	NDA 208254	NDA 020597
DMF [redacted] (b) (4)	DMF [redacted] (b) (4)	DMF [redacted] (b) (4)
DMF	DMF	DMF
DMF	DMF	

(as listed on FORM 356H – section 28, Cross References)

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2.3 Drug Formulation

The composition of the drug product is shown in Table 1 on a per mL and percentage basis. The netarsudil mesylate content is specified as the free base of the drug substance.

Table 1: Composition and Components of Netarsudil 0.02%/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**	**100%**

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)

(b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Pending CMC review

2.6 Proposed Clinical Population and Dosing Regimen

- Netarsudil/latanoprost Ophthalmic Solution is indicated for the reduction of elevated IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).
- The recommended dosage is one drop in the affected eye(s) once-daily in the evening.

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2.7 Regulatory Background

- Under IND 113064, Aerie Pharmaceuticals, Inc. is studying two ophthalmic products for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension: netarsudil ophthalmic solution 0.02% and PG324 ophthalmic solution, a fixed dose combination product containing netarsudil 0.02% and latanoprost 0.005%.

- The monotherapy, netarsudil ophthalmic solution 0.02% (Rhopressa®, NDA 208254) was approved on 12-18-2017.

- Type C meeting for guidance on the development of PG324 Ophthalmic Solution (FDC netarsudil/latanoprost ophthalmic solution) held on 6-5-2014.
    - Meeting minutes filed in DARRTS on 7-1-2014.
    - Meeting package submitted under SD # 27; nonclinical review filed in DARRTS on 5-21-2014.
    - Nonclinical team agreed the nonclinical package appeared adequate for NDA submission. We conveyed several recommendations for 3-month ocular toxicity study, ocular tissue distribution study, and clarified that without the right of reference, the applicant could only rely on information contained in the label for Xalatan® and/or the published literature.

- EOP2 meeting held on 4-15-2015 to discuss Phase 3 clinical trials and NDA submission for FDC product PG324 (AR-13324 0.02% and latanoprost 0.005%) Ophthalmic Solution.
    - Meeting minutes filed in DARRTS on 5-6-2015.
    - Meeting package submitted under SD # 52; nonclinical review filed in DARRTS on 3-17-2015.
    - Nonclinical team agreed nonclinical package appeared adequate for NDA submission. We conveyed the comment that a waiver request along with a justification for not conducting the carcinogenicity studies should be provided to the Division for consideration.

- Pre-NDA meeting held on 8-18-2018.
    - Meeting minutes filed in DARRTS on 9-10-2017.
    - Meeting package submitted under SD # 134; nonclinical review filed in DARRTS on 8-7-2017.
    - Nonclinical team agreed the nonclinical package appeared adequate for NDA submission. We conveyed several recommendations including the need for qualification of impurities that exceeded guidance limits and preference of using exposures multiples based on systemic exposure in the label. We requested a final clarification on the information from Xalatan® NDA the applicant was intending to rely on.

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3 Studies Submitted

3.1 Studies Reviewed

- Efficacy and Tolerability of 0.02% AR-13324 Ophthalmic Solution, Xalatan® Ophthalmic Solution, and a Fixed-Dose Combination of 0.02% AR-13324 and Latanoprost Following Topical Ocular Administration in Normotensive Formosan Rock Monkeys (Study # PG324-APH02)
- Ocular Tissue Distribution Study of Total Radioactivity in Dutch-Belted Male Rabbits Following a Single Topical Ocular Administration of [^{14}C/^{3}H]PG324 Ophthalmic Solution Compared to [^{14}C]AR-13324 Ophthalmic Solution 0.02% or [^{3}H]Latanoprost Ophthalmic Solution 0.005% (Study # PG324-APK01)
- A 3-Month Ocular Toxicity Study with PG324 Ophthalmic Solution in Dutch Belted Rabbits (Study # PG324-AS01)
- Neutral Red Uptake Phototoxicity Assay n BALB/c 3T3 Mouse Fibroblasts (Study # 17AF91.140053)
- Comparative Tolerability of 0.02% AR-13324 Ophthalmic Solution, Xalatan® Ophthalmic Solution, and Fixed-Dose Combination of 0.02% AR-13324 and Latanoprost Following Topical Ocular Administration in Dutch Belted Rabbits (Study # PG324-APH01)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- IND 113064 SD # 27 (filed in DARRTS on 5-21-2014)
- IND 113064 SD # 52 (filed in DARRTS on 3-17-2015)
- IND 113064 SD # 59 (filed in DARRTS on 9-2-2015)
- IND 113064 SD # 134 (filed in DARRTS on 8-7-2017)
- NDA 208254 Rhopressa® (filed in DARRTS on 11-6-2017)

4 Pharmacology

Netarsudil mesylate is a Rho-associated protein kinase (Rho kinase or ROCK) inhibitor. In nonclinical studies netarsudil ophthalmic solutions appear to reduce IOP through three mechanisms of action: increasing trabecular outflow facility, decreasing the production of aqueous humor, and reducing episcleral venous pressure (see nonclinical review NDA 208254, Rhopressa®).

Latanoprost is a prostaglandin F2α analogue. As a prostanoid selective FP receptor agonist, latanoprost is believed to reduce IOP by increasing the outflow of aqueous humor. Studies in animals and humans suggest that the main mechanism of action is increased uveoscleral outflow (Xalatan label, 12.1 Mechanism of Action).

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Both active ingredients are topical ophthalmic ester drugs and are converted by means of corneal esterases into an active metabolite.

Note: *Aerie also states that netarsudil is a norepinephrine transporter (NET) inhibitor. However, nonclinical data presented under NDA 208254 do not definitely support this mechanism of action for the current indication.*

4.1 Primary Pharmacology

Efficacy and Tolerability of 0.02% AR-13324 Ophthalmic Solution, Xalatan® Ophthalmic Solution, and a Fixed-Dose Combination of 0.02% AR-13324 and Latanoprost Following Topical Ocular Administration in Normotensive Formosan Rock Monkeys (Study # PG324-APH02, Module 4.2.1.1, non-GLP) - The purpose of this study was to compare the ocular efficacy and tolerability of 0.02% AR-13324 Ophthalmic Solution, Xalatan® Ophthalmic Solution (0.005% latanoprost), and an AR-13324 0.02%/latanoprost 0.005% FDC (PG324 Ophthalmic Solution) in normotensive Formosan Rock monkeys (n=6 males/group). The test articles were administered topically once in the morning for 3 days to one eye of each rabbit; the contralateral eye served as an untreated control. Each dose was administered just after the 0-, 24-, and 48-hour measurement of IOP. IOP was measured in both eyes at 4, 8, 24, 48, 52, 56, and 72 hours after baseline (t=0) IOP measurement. Ocular irritation (Draize scoring system) was assessed prior to each IOP measurement.

All three formulations produced statistically significant ($p<0.01$) reductions in IOP as compared to the contralateral control eye (Figure 1).

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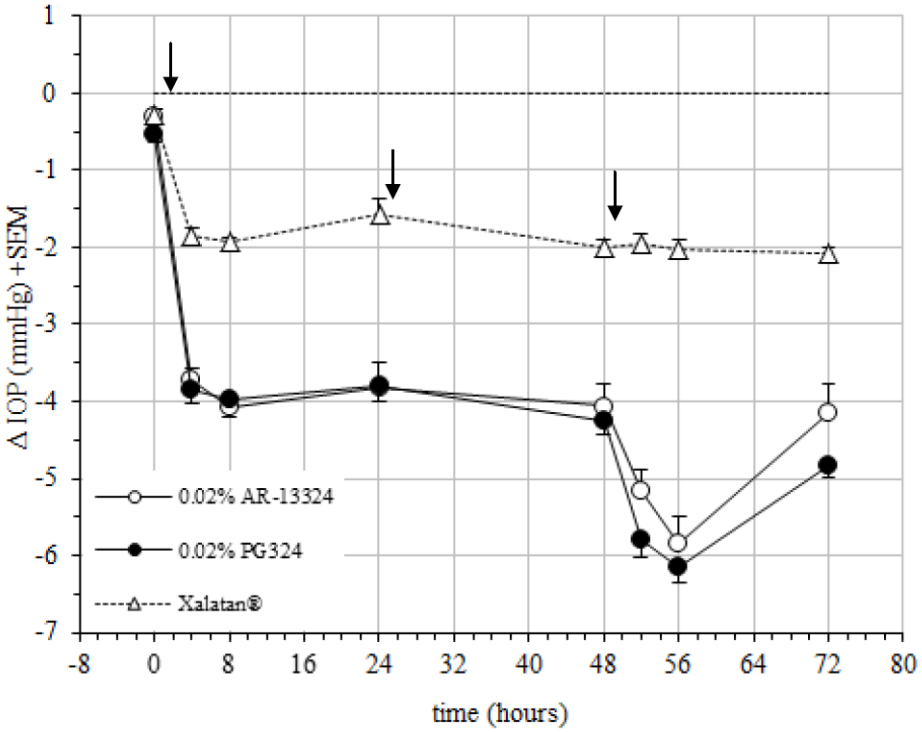
Figure 1: Mean reduction in Intraocular Pressure (ΔIOP) following Administration of 0.02% AR-13324 Ophthalmic Solution, Xalatan® Ophthalmic Solution, or 0.02% PG324 Ophthalmic Solution in Normotensive Formosan Rock Monkeys



The FDC produced substantially larger IOP reductions than Xalatan® Ophthalmic Solution. The FDC also showed increased efficacy compared to 0.02% AR-13324 alone at later timepoints (after the 3rd dose on Day 3 [48 hours post initial dose]). Following the final dose on Day 3, mean IOP reductions ranged from 2.0 to 2.1 mmHg for Xalatan® Ophthalmic Solution, 4.1 to 5.8 mmHg for 0.02% AR-13324 Ophthalmic Solution, and 4.3 to 6.2 mmHg for 0.02% PG324 Ophthalmic Solution throughout the remainder of the study. No ocular irritation was observed in any of the treatment groups.

4.3 Safety Pharmacology

No studies were conducted with the combination. In cardiovascular safety studies conducted with netarsudil in dogs (NDA 208254), findings included redness in various body parts and decreased blood pressure associated with an increased heart rate. These are expected pharmacological actions of Rho kinase inhibitors. Rho kinase inhibitors reduce blood pressure by decreasing vascular wall smooth muscle contractility and thereby reducing vascular tone, causing vasodilation. The redness is a sign of peripheral vasodilation. The NOAEL for these findings (0.7 mg/kg free base, IV) provided an exposure margin of at ~270X (based on C_{max}). Based on the observed clinical exposure of netarsudil generally below the lower limit of quantitation of 0.100 ng/mL at the recommended clinical dose, it is unlikely these findings may have significant clinical relevance.

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5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Note: *A brief review of this study was conducted by this reviewer under IND 113064 SD # 59 (filed in DARRTS on 9-2-2015)*

Ocular Tissue Distribution Study of Total Radioactivity in Dutch-Belted Male Rabbits Following a Single Topical Ocular Administration of [^{14}C/^{3}H]PG324 Ophthalmic Solution Compared to [^{14}C]AR-13324 Ophthalmic Solution 0.02% or [^{3}H]Latanoprost Ophthalmic Solution 0.005% (non-GLP) (Study # PG324-APK01) - Male Dutch-Belted rabbits were given a single topical ocular dose (35 µL) per eye of [^{14}C/^{3}H]PG324 ([^{14}C]AR-13324/[^{3}H]latanoprost), 0.02% [^{14}C]AR-13324 or 0.005% [^{3}H]latanoprost. Ocular tissue distribution was evaluated at 0.25, 0.5, 1, 4, 8 and 24 hours postdose in 3 rabbits/timepoint.

In general, the rank order of [^{14}C]AR-13324-related radioactivity concentrations following topical ocular administration of [^{14}C/^{3}H]PG324 was cornea >conjunctiva >iris/ciliary body >retina-choroid-plexus >aqueous humor >vitreous humor >lens. This rank order of ocular tissue [^{14}C]AR-13324 radioactivity was the same following topical ocular administration of [^{14}C]AR-13324. In general, [^{14}C]AR-13324 mean elimination half-lives ranged from 8.6 to 51 hours in the FDC group and 3.3 to 458 hours when given alone.

Quantitatively, [^{14}C]AR-13324-related radioactivity in the conjunctiva, iris/ciliary body, and lens were 5.8x, 2x, and 1.6x higher when AR-13324 was given alone compared to the FDC PG324, based on mean AUC_{last}.

In general, the rank order of ocular [^{3}H]latanoprost-related radioactivity concentrations following topical ocular administration of [^{14}C/^{3}H]PG324 was cornea »aqueous humor ≈iris/ciliary body >conjunctiva >retina-choroid plexus > lens ≈vitreous humor. This rank order of ocular tissue [^{3}H]latanoprost-related radioactivity was the same following topical ocular administration of [^{3}H]latanoprost. In general, [^{3}H]latanoprost mean elimination half-lives ranged from 2.1 to 15.6 hours in the FDC group and 2.0 to 12.4 hours when given alone.

Quantitatively, the radioactivity in the conjunctiva and vitreous was 2x and 3x higher when latanoprost was given alone compared to FDC PG324, based on mean AUC_{last}. However, the data in the vitreous is considered equivocal as the duplicates had very different AUC_{last} values with one of the samples showing levels comparable to those observed in the FDC group and the other ~6X higher.

No significant difference was observed in blood or plasma levels of [^{14}C]AR-13324- or [^{3}H]latanoprost-related radioactivity when given in the FDC formulation or each active component formulation alone. Overall, [^{14}C]AR-13324 C_{max} values were ≤1.86 ng-eq/g

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and AUC_{last} values were ≤9.25 ng-eq•hr/g; [^{3}H]latanoprost C_{max} values were ≤1.84 ng-eq/g and AUC_{last} values were ≤1.47 ng-eq•hr/g.

Table 2 summarizes the PK parameters for AR-13324 in the ocular tissues, blood, and plasma when given in the FDC formulation (Group 1) and when given alone (Group 2). Table 3 summarizes the PK parameters for latanoprost when given in the FDC formulation (Group 1) and when given alone (Group 3).

In summary, the data from the ocular tissue distribution study suggest that no toxicologically relevant differences in ocular tissue distribution and plasma PK profiles are to be expected after topical ocular administration of PG324 Ophthalmic Solution compared to each active component of the combination alone.

Table 2: Pharmacokinetic Parameters For [^{14}C]AR-13324 in Blood, Plasma, and Ocular Tissues Following a Single Topical Ocular Dose of [^{14}C/^{3}H]PG324 or [^{14}C]AR-13324 Dosing Solution into Both Eyes

			[^{14}C]AR-13324									
Sample Type	Group	Eye	C_{max} (ng*eq/g)	T_{max} (hr)	C_{last} (ng*eq/g)	T_{last} (hr)	AUC_{last} (ng*eq*hr/g)	$AUC_{0\text{-}inf}$ (ng*eq*hr/g)	$T_{1/2,e}$ (hr)	Cl/F (g/hr)	V_z/F (g)	MRT (hr)
Conjunctiva	1	L	3143	0.25	146	24	9601	11714	11	0.85	13.2	12
Conjunctiva	1	R	2746	0.25	99.0	24	9253	10454	8.6	0.96	11.8	9.4
Conjunctiva	2	L	2917	0.25	158	24	15297	16989	7.8	0.59	6.6	8.8
Conjunctiva	2	R	8327	8	280	24	93594	94914	3.3	0.11	0.50	8.1
Cornea	1	L	5174	0.5	1340	24	66235	88608	12	0.11	1.94	17
Cornea	1	R	4334	8	1171	24	74121	93986	11	0.11	1.71	15
Cornea	2	L	5697	1	1778	24	75959	116019	16	0.086	2.0	22
Cornea	2	R	4437	8	1951	24	81128	139244	20	0.072	2.0	28
Aqueous Humor	1	L	36.4	8	22.0	24	659	1358	22	7.4	234	34
Aqueous Humor	1	R	36.9	8	19.8	24	607	1116	18	9.0	230	29
Aqueous Humor	2	L	32.9	8	20.2	24	581	1244	23	8.0	264	36
Aqueous Humor	2	R	31.6	8	22.8	24	580	1698	34	5.9	289	52
Iris / Ciliary Body	1	L	442	0.5	274	24	4484	x	x	x	x	x
Iris / Ciliary Body	1	R	355	0.5	242	24	4738	x	x	x	x	x
Iris / Ciliary Body	2	L	1756	1	595	24	9991	x	x	x	x	x
Iris / Ciliary Body	2	R	648	4	333	24	8077	25710	41	0.39	23	61
Lens	1	L	1.67	0.25	0.973	24	21.8	94.5	58	106	8872	86
Lens	1	R	1.63	0.25	1.19	24	23.6	x	x	x	x	x
Lens	2	L	7.76	0.25	1.46	24	34.6	938	458	10.7	7044	660
Lens	2	R	2.54	0.5	1.31	24	36.5	105	36	95.3	4974	54
Vitreous Humor	1	L	6.18	0.25	1.88	24	63.5	144	29	69.7	2942	41
Vitreous Humor	1	R	5.04	0.5	1.69	24	47.0	226	73	44.3	4694	105
Vitreous Humor	2	L	4.56	1	1.17	24	49.6	85.1	21	117	3514	28
Vitreous Humor	2	R	5.21	1	2.31	24	70.0	175	33	57.0	2727	47

x Could not be determined from the concentration-time data.

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Continuation Table 2:

			[^{14}C]AR-13324									
Sample Type	Group	Eye	C_{max} (ng*eq/g)	T_{max} (hr)	C_{last} (ng*eq/g)	T_{last} (hr)	AUC_{last} (ng*eq*hr/g)	$AUC_{0\text{-}inf}$ (ng*eq*hr/g)	$T_{1/2,e}$ (hr)	Cl/F (g/hr)	V_z/F (g)	MRT (hr)
Retina-Choroid-Plexus	1	L	114	0.5	19.1	24	684	1902	42	5.3	320	58
Retina-Choroid-Plexus	1	R	67.1	1	24.8	24	811	2667	51	3.8	274	71
Retina-Choroid-Plexus	2	L	229	1	37.3	24	1522	3143	30	3.2	137	39
Retina-Choroid-Plexus	2	R	67.4	0.25	29.3	24	923	1994	26	5.0	186	38
Blood	1		1.14	0.5	0.121	24	6.26	8.60	14	2326	47747	17
Plasma	1		1.53	0.5	0.0966	24	7.18	8.51	10	2350	34245	11
Blood	2		1.59	0.5	0.154	24	7.44	11.8	20	1691	49409	24
Plasma	2		1.86	0.5	0.108	24	9.25	11.0	11	1818	29076	11

Table 3: Pharmacokinetic Parameters For [^{3}H]Latanoprost in Blood, Plasma, and Ocular Tissues Following a Single Topical Ocular Dose of [^{14}C/^{3}H]PG324 or [^{3}H]Latanoprost Dosing Solution into Both Eyes

			[^{3}H]Latanoprost									
Sample Type	Group	Eye	C_{max} (ng*eq/g)	T_{max} (hr)	C_{last} (ng*eq/g)	T_{last} (hr)	AUC_{last} (ng*eq*hr/g)	$AUC_{0\text{-}inf}$ (ng*eq*hr/g)	$T_{1/2,e}$ (hr)	Cl/F (g/hr)	V_z/F (g)	MRT (hr)
Conjunctiva	1	L	129	0.25	0.384	24	124	128	6.1	13.7	120	3.4
Conjunctiva	1	R	124	0.25	1.99	24	158	174	8.1	10.0	117	7.2
Conjunctiva	3	L	270	0.5	0.910	24	278	284	5.3	6.17	46.8	3.2
Conjunctiva	3	R	164	0.25	2.22	24	292	314	7.8	5.57	62.8	6.2
Cornea	1	L	2572	0.25	1.53	24	6342	6347	2.5	0.28	1.0	2.5
Cornea	1	R	1730	0.25	2.51	24	5203	5214	2.9	0.34	1.4	3.2
Cornea	3	L	2344	0.5	1.91	24	6112	6119	2.7	0.29	1.1	2.7
Cornea	3	R	1574	0.25	6.86	24	4937	4970	3.8	0.35	1.9	3.1
Aqueous Humor	1	L	94.2	4	0.102	24	590	590	2.1	2.96	9.0	4.2
Aqueous Humor	1	R	68.1	4	0.116	24	584	584	2.2	3.00	9.4	4.6
Aqueous Humor	3	L	97.0	1	0.0669	24	589	589	2.0	2.97	8.6	3.9
Aqueous Humor	3	R	95.9	4	0.106	24	648	648	2.1	2.70	8.2	4.0
Iris / Ciliary Body	1	L	180	0.5	0.248	24	511	512	2.8	3.41	13.6	3.2
Iris / Ciliary Body	1	R	145	0.5	0.323	24	488	490	2.9	3.57	15.1	4.2
Iris / Ciliary Body	3	L	114	1	0.262	24	532	533	2.7	3.28	12.8	3.6
Iris / Ciliary Body	3	R	108	1	0.386	24	630	631	2.8	2.77	11.1	4.1
Lens	1	L	1.04	4	0.354	24	12.8	20.3	15.6	86.2	1944	23
Lens	1	R	2.78	0.25	0.275	24	15.6	19.3	9.3	90.7	1219	14
Lens	3	L	1.56	0.5	0.305	24	15.9	20.4	10.3	85.7	1268	16
Lens	3	R	1.44	0.5	0.277	24	13.9	18.8	12.4	93.3	1669	17
Vitreous Humor	1	L	3.16	0.25	0.0120	24	8.7	8.7	3.5	200	1004	3.4
Vitreous Humor	1	R	1.54	0.5	0.0271	24	6.0	6.2	5.2	283	2108	5.1
Vitreous Humor	3	L	3.79	8	0.0094	24	43	43	2.8	40.9	165	7.4
Vitreous Humor	3	R	1.77	0.5	0.0399	24	8.0	8.3	5.9	211	1797	5.5

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Continuation Table 3:

Sample Type	Group	Eye	C_{max} (ng*eq/g)	T_{max} (hr)	C_{last} (ng*eq/g)	T_{last} (hr)	AUC_{last} (ng*eq*hr/g)	AUC_{0-inf} (ng*eq*hr/g)	$T_{1/2,e}$ (hr)	Cl/F (g/hr)	V_z/F (g)	MRT (hr)
			[^{3}H]Latanoprost									
Retina-Choroid-Plexus	1	L	56.1	0.5	0.0389	24	118	118	2.5	14.8	54.4	3.0
Retina-Choroid-Plexus	1	R	39.2	0.5	0.100	24	134	134	3.0	13.0	56.0	3.7
Retina-Choroid-Plexus	3	L	43.6	0.25	0.150	24	121	122	3.5	14.4	73.0	3.6
Retina-Choroid-Plexus	3	R	26.8	1	0.0961	24	139	140	2.9	12.5	52.6	3.8
Blood	1		0.593	0.25	0.0095	24	0.69	0.77	8.9	4535	57953	8.0
Plasma	1		1.37	0.25	0.0209	24	1.33	1.54	10.1	2275	33109	9.2
Blood	3		0.995	0.25	0.0041	24	0.90	0.95	7.4	3704	39797	4.6
Plasma	3		1.84	0.25	0.0024	24	1.47	1.49	4.8	2356	16205	2.5

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 3-Month Ocular Toxicity Study with PG324 Ophthalmic Solution in Dutch Belted Rabbits (GLP)

Note: *A brief review of this study was conducted by this reviewer under IND 113064 SD # 59 (filed in DARRTS on 9-2-2015)*

Study no.:	PG324-AS01
Study report location:	EDR Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 9, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PG324 Ophthalmic Solution (0.02% AR-13324, 0.005% latanoprost), lot # 1590646, 99% label claim for netarsudil, 94% label claim for latanoprost (per Certificate of Analysis at release dated 1-21-14)

Key Study Findings

- In both the once daily and twice daily PG324 Ophthalmic Solution treatment groups, mild to moderate redness of the conjunctiva and/or sclera was observed. The finding occurred sporadically and did not persist through the recovery period.
- Transient decreases in IOP (the expected pharmacological activity) were observed at both test article doses.

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- The highest dose tested, 0.02% AR-13324/0.005% latanoprost BID, was considered as the NOAEL.

Methods

Doses:	0, 0.02%/0.005% QD, and 0.02%/0.005% BID netarsudil (AR-13324)/latanoprost (0, 0.014/0.004, and 0.028/0.007 mg/day, respectively)
Frequency of dosing:	Both eyes were dosed QD (once daily) or BID (twice daily [8 hours apart ± 20 minutes]) for 3 months
Route of administration:	Topical ocular
Dose volume:	~0.035 mL
Formulation/Vehicle:	AR-13324 Ophthalmic Solution Placebo
Species/Strain:	Dutch-Belted Rabbit
Number/Sex/Group:	7 Five animals/sex/group were euthanized at the completion of the dosing phase. Two animals/sex/group remained on study, untreated, for a 2-week recovery period.
Age:	Approximately 5-10 months old
Weight:	2.0 to 2.8 kilograms
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None with an impact on the interpretation of the data

Observations and Results

Mortality (2x/day)

None

Clinical Signs (2x/day)

Mild to moderate redness of the eyes (conjunctiva and/or sclera) was noted sporadically during the dosing phase in control (1 out of 7 males, 0 out of 7 females), low-dose (7 out of 7 males, 7 out of 7 females) and high-dose (7 out of 7 males, 6 out 7 females) animals. Clear or white ocular discharge was observed sporadically throughout the dosing phase in control (1 out of 7 males, 0 out of 7 females) and high-dose (0 out of 7 males, 2 out of 7 females) animals. On Day 91, the day following the final dose but prior to the terminal necropsy, mild conjunctival redness was noted in low-dose (4 out of 7 males, 0 out of 7 females) and high-dose (1 out of 7 males, 0 out of 7 females) animals.

All eyes were normal on Days 93-105 of the recovery period.

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Body Weights (Prestudy, Day 1, and once weekly thereafter)

No test article-related effects

Feed Consumption (Daily; quantitatively)

No test article-related effects

Ocular Observations (Daily; scored according to Draize scoring system once prior to treatment initiation, postdose on Days 1, 7 and 90, and during the final week of the recovery phase)

Slight conjunctival redness was observed. In the Study Report, it is stated that the Draize scores were related to minor conjunctival irritation. However, the conjunctival redness could also be related to a pharmacological effect (dilation of conjunctival blood vessels) of the test article. The Draize scores for redness of the conjunctiva were as follows:

- On Day 1, scores of 1 were recorded bilaterally at the low dose (2 out of 7 females), and high dose (7 out of 7 males, 6 out of 7 females).
- On Day 7, scores of 1 were recorded bilaterally in control group (1 out of 7 males), low dose (1 out of 7 males), and high dose (2 out of 7 females).
- On Day 90, scores of 1 were recorded bilaterally for conjunctival redness at the low dose (5 out of 7 males, 5 out of 7 females). In addition, scores of 2 were recorded bilaterally for conjunctival redness at the low dose (2 out of 7 males, 1 out of 7 females).
- On Day 101/102 of the recovery phase, all scores recorded were 0 (i.e., the eyes appeared normal).

Ophthalmoscopy (Indirect ophthalmoscopy and slit lamp [McDonald-Shadduck scoring system] before treatment initiation, towards the end of Week 1, approximately half way through Week 4, towards the end of Week 12 of the dosing phase, and during the final week of the recovery period)

At Week 4, conjunctival discharge (score 1) was noted in the right eye of one high-dose female. Based on the single incidence, the relationship to treatment of this finding is unclear. No other test article-related finding was observed.

IOP (Prior to treatment initiation, towards the end of Weeks 1, 4 and 12, and during the final week of the recovery period)

Decreased mean IOP (the expected pharmacological activity) was noted in low-dose and high-dose females on Day 7, with statistical significance only observed for the left eye (-19%) in low-dose females. On Day 28, a slight decrease in mean IOP values was noted in high-dose males with statistical significance only observed for the right eye (-32%). No differences were observed in mean IOP values with continued dosing.

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Electroretinograms (ERGs) (Scotopic and photopic ERGs and visual evoked response/potential [VER/VEP] prior to treatment initiation, during Week 12 and for recovery animals, towards the end of the recovery period) –

No test-article related effects were apparent in ERG evaluations. Per summary information, no test article-related effects were observed in VER/VEP (data not shown).

Hematology and Coagulation (Prior to treatment initiation and on Days 91 and 105) – At recovery, high-dose males showed a decrease in mean APTT, compared to controls (26%) or baseline (24%). P. 226

On Day 91, mean activated partial thromboplastin time (APTT) was statistically significantly lower than control group in mid- and high-dose females. The mean value was also lower in high-dose males at the end of the recovery period. However, the mean values were comparable to baseline and/or were within the range of historical control data. Therefore, the changes do not appear related to the test article.

Clinical Chemistry (Prior to treatment initiation and on Days 91 and 105)

No test article-related effects

Gross Pathology (End of dosing [Day 91] and end of recovery [Day 105)

No test article-related findings

Organ Weights (Adrenals, brain, heart, kidneys, liver, testes, ovaries, spleen, and thyroids/parathyroids)

Statistically significantly lower mean absolute and relative (to body weight and brain weight) spleen weights were observed at both PG324 Ophthalmic Solution doses in males compared to controls (28-34%; non-dose dependent). A trend toward lower mean spleen weight was observed in females. At the end of recovery, spleen weight was comparable to controls.

This finding was not observed in the 3/6/9-month ocular toxicity studies in rabbits and monkeys or in 28-day IV toxicity studies in rats and dogs with AR-13324 (see NDA 208254 nonclinical review) or reported in studies conducted for latanoprost (Latanoprost Action Package). Therefore, the finding appeared to be of no toxicological relevance.

Histopathology (Eyes with bulbar conjunctiva, optic nerve, eyelids with palpebral conjunctiva and meibomian glands, nictitating membrane, harderian gland, and lacrimal gland)

Adequate Battery – Yes (see reviewer's comment under "Toxicokinetics" below)

Peer Review - No

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Histological Findings – No test article-related findings

Toxicokinetics

We had previously agreed (nonclinical review SD # 27 review, filed in DARRTS on 5-21-2014) that TK measurements and systemic tissue histopathology evaluations were not necessary in this study because no significant systemic exposure of AR-13324, enantiomer AR-13323, and main metabolites was observed at dose levels of up to 0.04% BID administered daily in the rabbit for 3-months. Plasma levels in the previous 3-month ocular toxicity study were near the lower limit of quantitation of 1 ng/mL and observed only at the 0.5 to 1 hr timepoint (2.90 ng/mL for AR-13324 on Week 12 at 0.5 hr; 1.02-1.60 ng/mL for metabolite AR-13503 on Day 1). In addition, the data from the ocular tissue distribution study suggest that no toxicologically relevant differences in ocular tissue distribution and plasma PK profiles are to be expected after topical ocular administration of PG324 Ophthalmic Solution compared to each active component of the combination alone.

In intravenous toxicity studies of 28-day duration at netarsudil doses up to 0.7 mg/kg/day in rats and dogs, there were no systemic toxicities. The mean plasma exposures at the highest dose were 64 ng/mL (C_{max}) and 126 ng•hr/mL (AUC_{0-24hr}) in rats and 63 ng/mL (C_{max}) and 482 ng•hr/mL (AUC_{0-24hr}) in dogs. Based on C_{max}, the exposure margins are >60-fold for the plasma levels observed in the 1-month and 3-month ocular toxicity studies with netarsudil.

Dosing Solution Analysis

Stability data for up to 12 months showed both APIs are stable in the ophthalmic formulation (99.3% for netarsudil and 95.8% for latanoprost at Month 12).

7 Genetic Toxicology

No genetic toxicity studies were conducted with the combination. The applicant conducted genetic toxicity studies with netarsudil under the program for Rhopressa®. Netarsudil did not show mutagenic or clastogenic potential in the full battery of genetic toxicity studies conducted.

For latanoprost, Aerie is relying on the information on the current Xalatan label (approved April 10, 2017). Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional in vitro and in vivo studies on unscheduled DNA synthesis in rats were negative.

The language in section 13.1 “Carcinogenesis, Mutagenesis, Impairment of Fertility” of the proposed label contains the previously approved information for both Rhopressa® and Xalatan®.

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8 Carcinogenicity

Aerie submitted a waiver request for carcinogenicity studies for netarsudil 0.02%/latanoprost 0.005% ophthalmic solution (Module 1.12.5). A waiver of carcinogenicity studies was granted for Rhopressa® (netarsudil ophthalmic solution 0.02%) NDA 208254. The current justification for omitting the studies is similar to that submitted for Rhopressa® and lists the following observations:

- Low systemic exposure of netarsudil, its enantiomer and metabolites (close to the lower limit of quantitation of <1 ng/mL) observed in animal studies following ocular administration
- Low systemic exposure of netarsudil in a Phase 1 study in healthy volunteers (below the lower limit of quantitation of <0.100 ng/mL)
    - Only 1 plasma sample from 1 subject had a concentration above the LLOQ for the primary metabolite of netarsudil (0.11 ng/mL).
- No signs of pre-neoplastic lesions following chronic repeated dosing in a 6-month topical ocular toxicity study in rabbits (Study # AR-13324-AS13) and a 9-month topical ocular toxicity study in primates (Study # AR-13324-AS14)
- No evidence of long-term tissue retention of parent compound or metabolite(s) resulting in local tissue reactions or other pathophysiological responses in the ocular tissue distribution studies in Dutch Belted rabbits (AR-13324-APK03) and the mass balance/autoradiography study after IV dose in pigmented rats (AR-13324-APK04)

Regarding this last statement, the half-life in some ocular and systemic tissues was over 7 days long in studies conducted under NDA 208254. Therefore, this reviewer made the following observations under the review of NDA 208254:

- The ocular tissue distribution studies in Dutch Belted rabbits (Study # AR-13324-APK03) showed slower terminal elimination in retina-choroid-plexus, lens and iris/ciliary body (with $t_{1/2,e}$ values ranging from 68 to 204 hours) after a single topical dose. However, these tissues did not show indications of local tissue reactions or other pathophysiological responses in the long-term ocular toxicity studies.
- A single IV dose mass balance/autoradiography study in pigmented rats (Study # AR-13324-APK04) showed radioactivity in some tissues persisted throughout the duration of the study (168 hours). These tissues included the adrenal gland cortex, lung, liver, adrenal gland medulla, preputial gland, eye uvea, exorbital lacrimal gland, and intra-orbital gland. However, the long-term ocular toxicity studies did not show local tissue reactions or other pathophysiological responses in these tissues.

Regarding latanoprost, the applicant cited the information in the Xalatan® label, which indicates that latanoprost was not carcinogenic in mice or rats at doses 2800X the recommended maximum human dose.

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Based on the observations listed above, this reviewer agrees carcinogenicity evaluation is not necessary for netarsudil 0.02% /latanoprost 0.005% ophthalmic solution at the intended dosing regimen. The language in section 13.1 "Carcinogenesis, Mutagenesis, Impairment of Fertility" of the proposed label contains the previously approved information for both Rhopressa® and Xalatan®.

9 Reproductive and Developmental Toxicology

The applicant conducted embryofetal development toxicity studies with netarsudil under the program for Rhopressa®. Systemic administration (IV) of netarsudil mesylate to pregnant rats and rabbits resulted in embryofetal toxicity. The NOAEL for these findings was 40X (rats) and 214X (rabbits) the plasma exposure at the recommended human ophthalmic dose (based on C_{max}).

For latanoprost, Aerie is relying on the information on the current Xalatan® label (approved April 10, 2017). Latanoprost produced embryofetal lethality at 80X the recommended human ophthalmic dose. The NOAEL for these findings was 15X the recommended human ophthalmic dose.

The language in section 8.1 "Pregnancy" of the proposed label contains the previously approved information for both Rhopressa® and Xalatan®.

10 Special Toxicology Studies

Neutral Red Uptake Phototoxicity Assay n BALB/c 3T3 Mouse Fibroblasts (Study # 17AF91.140053, Module 4.2.3.7.7, GLP) – AR-13324 (0.490 to 30 µg/mL ± UVA) was not predicted to have phototoxic potential, i.e., Photoirritancy Factor (PIF) < 2.0 and Mean Photo Effect (MPE) < 0.1. The positive control (chlorpromazine) PIF and MPE values (mean of 19.5 and 0.538, respectively) were within criteria for a valid test.

Comparative Tolerability of 0.02% AR-13324 Ophthalmic Solution, Xalatan® Ophthalmic Solution, and Fixed-Dose Combination of 0.02% AR-13324 and Latanoprost Following Topical Ocular Administration in Dutch Belted Rabbits (Study # PG324-APH01, Module 4.2.1.1, non-GLP) - The purpose of this study was to compare the ocular tolerability of 0.02% AR-13324 Ophthalmic Solution, Xalatan® Ophthalmic Solution (0.005% latanoprost), and an AR-13324 0.02%/latanoprost 0.005% FDC in normotensive Dutch-Belted rabbits (n=4 males/group). The test articles were administered topically once in the morning for 3 days to one eye of each rabbit; the contralateral eye served as an untreated control. The tolerability scores (Draize method) were determined on each day at times 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 8 and 24 hours postdose. Reduction of IOP (expected pharmacological activity) was not evaluated because rabbits are not a good model for studying the ocular hypotensive effect of prostaglandin analogs.

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All 3 formulations produced only trace (Draize score 0.1 to 0.5) hyperemia (conjunctival redness) after each daily dose, which resolved within 24 hours postdose on Day 1 and within 8 hours postdose on Days 2 and 3. No other sign of irritation was observed. Therefore, the FDC of AR-13324 and latanoprost (PG324 Ophthalmic Solution), was well tolerated and produced hyperemia comparable to that observed after treatment with 0.02% AR-13324 Ophthalmic Solution or Xalatan® Ophthalmic Solution alone.

11 Integrated Summary and Safety Evaluation

Netarsudil/latanoprost ophthalmic solution 0.02%/0.005% is a fixed-dose combination (FDC) of two FDA-approved ocular hypotensive active components, netarsudil 0.02% and latanoprost 0.005%. This NDA has been filed as a 505(b)(2) application relying in the applicant's nonclinical package for Rhopressa® (netarsudil 0.02% ophthalmic solution, NDA 208254) and the FDA's findings of safety and effectiveness for Xalatan® (NDA 020597), specifically, the currently approved Xalatan® prescribing information (approved April 10, 2017).

In order to bridge the nonclinical program of the FDC product to that of Rhopressa® and Xalatan®, Aerie conducted a comparative ocular tissue distribution study in rabbits. In addition, the FDC product was evaluated in a 3-month repeat-dose ocular toxicity study in rabbits and comparative 3-day ocular tolerability studies in rabbits and monkeys.

In the ocular tissue distribution study in rabbits administered radiolabeled compounds, there was no toxicologically relevant differences in the ocular tissue distribution of netarsudil (AR-13324)- and latanoprost-related radioactivity whether netarsudil 0.02% and latanoprost 0.005% were administered separately or together as netarsudil 0.02%/latanoprost 0.005% ophthalmic solution. No significant difference was observed in blood or plasma levels of netarsudil- or latanoprost-related radioactivity when given in the combination or each active component alone.

In the ocular tolerability studies, normotensive rabbits and monkeys received a topical administration of netarsudil (AR-13324 Ophthalmic Solution 0.02%), Xalatan® Ophthalmic Solution (latanoprost 0.005%), or the FDC product (identified as AR-13324 0.02%/latanoprost 0.005% or PG324 Ophthalmic Solution) once daily for 3 days. In the rabbit, all 3 formulations produced comparable trace and transient conjunctival hyperemia (conjunctival redness). 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 the monkey, hyperemia or any signs of ocular irritation were not observed with any formulation. However, the FDC produced substantially larger IOP reductions (the expected pharmacological activity) compared to Xalatan®. The FDC also showed increased efficacy compared to netarsudil 0.02% at later timepoints (after the 3rd daily dose on Day 3).

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The FDC product (identified as PG324 Ophthalmic Solution) was well-tolerated in the 3-month rabbit ocular toxicity study with no unexpected adverse findings. Findings were limited to mild to moderate redness of the conjunctiva and/or sclera and transient decreases in IOP. The hyperemia was observed sporadically and did not persist through the recovery period. These findings have been previously observed in ocular toxicity studies conducted with netarsudil (see nonclinical review for NDA 208254). The NOAEL was the high dose, netarsudil 0.02%/latanoprost 0.005% BID, providing an exposure margin of 2X the intended clinical dose regimen (i.e., QD).

Netarsudil was not phototoxic in the 3T3 neutral red uptake assay. Carcinogenicity studies were not conducted. The justification provided by the applicant to omit these studies was considered acceptable (see Section 8. Carcinogenicity).

In conclusion, the data of the comparative PK and tolerability studies, as well as the 3-month ocular toxicity study conducted with the FDC product provide an adequate bridge to the nonclinical program of Rhopressa® and Xalatan®. Therefore, the nonclinical data presented in this NDA provide adequate safety support for the intended dosing regimen of netarsudil 0.02%/latanoprost 0.005% ophthalmic solution of once daily for the indication of reduction of IOP. This reviewer recommends approval of the NDA.

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/s/

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01/23/2019 04:02:06 PM

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