

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208254Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208254
PDUFA Goal Date	February 28, 2018
OSE RCM #	2017-545
Reviewer Name	Erin M. South, PharmD, DRISK
Team Leader	Donella Fitzgerald, PharmD, DRISK
Deputy Division Director	Jamie Wilkins Parker, PharmD, DRISK
Review Completion Date	December 18, 2017
Subject	Evaluation of Need for a REMS
Established Name	Netarsudil
Trade Name	Rhopressa
Name of Applicant	Aerie Pharmaceuticals, Inc.
Therapeutic Class	Rho kinase inhibitor
Formulation	0.02% ophthalmic solution
Dosing Regimen	One drop administered to affected eye(s) once a day, in the evening

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rhopressa (netarsudil) is necessary to ensure the benefits of this product outweigh its risks. On February 28, 2017, Aerie Pharmaceuticals, Inc. (hereinafter, referred to as Aerie or the Applicant) submitted a New Drug Application (NDA 208254) for netarsudil with the proposed indication of the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension (OHT) or open-angle glaucoma (OAG). The risks associated with the use of netarsudil include bacterial keratitis and corneal verticillata. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Transplant and Ophthalmology Products (DTOP) agree that a REMS is not needed to ensure the benefits of netarsudil 0.02% ophthalmic solution outweigh its risks. Netarsudil has proven to reduce the severity of elevated IOP in patients with OHT or OAG. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required. Furthermore, ophthalmology healthcare providers who treat OHT and OAG, in general, are informed of these risks as there are similar adverse events associated with exposure to other ophthalmologic treatments for OHT or OAG.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rhopressa (netarsudil) is necessary to ensure the benefits of this product outweigh its risks. On February 28, 2017, Aerie Pharmaceuticals, Inc. (hereinafter, referred to as Aerie or the Applicant) submitted a New Drug Application (NDA 208254, Rhopressa) for netarsudil ophthalmic solution 0.02%. The proposed indication is for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension (OHT) or open-angle glaucoma (OAG). This application is under review in the Division of Transplant and Ophthalmology Products (DTOP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Netarsudil, an NME [505 (b)(1)],^a is a Rho kinase (ROCK) inhibitor. ROCK inhibitors represent a new class of medications that lower IOP. The proposed proprietary name is Rhopressa and proposed indication is for the reduction of elevated IOP in patients with OAG or OHT. The Applicant proposes that netarsudil lowers IOP by multiple mechanisms of action, that include increasing trabecular outflow facility, decreasing the production of aqueous humor, and reducing episcleral venous pressure. The proposed

^a FDAAA factor (F): Whether the drug is a new molecular entity

to-be-marketed netarsudil formulation and strength is as an ophthalmic solution containing 0.02 mg/mL of netarsudil (equivalent to 0.28 mg of netarsudil dimesylate), available in a multiple-dose vial. Netarsudil would be used mainly in an outpatient setting. The proposed dosing regimen is one drop administered to the affected eye(s) once daily in the evening; and the treatment duration is indefinite.^b

Netarsudil is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208254 relevant to this review:

- 2/28/2017: NDA 208254 submission for netarsudil ophthalmic solution indicated for the treatment of elevated IOP in patients with OHT or OAG received.
- 7/25/2017: The Mid-Cycle Communication Meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that, based on the currently available data, there were no safety issues that require a REMS for netarsudil. However, the Agency indicated that the potential safety risk of cornea verticillata/corneal opacities was still under review. Potential risk management actions would be discussed at the October 13, 2017 Advisory Committee (AC) Meeting.
- 9/29/17: The Late-Cycle Meeting was held between the Agency and Applicant via teleconference. The Agency informed the Applicant that, based on the currently available data, no new safety issues had been identified to date, other than those previously identified at the Mid-Cycle Meeting held on July 25, 2017.
- 10/13/2017: A meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC or AC) was convened to discuss the safety and efficacy of NDA 208254. The AC unanimously agreed that the clinical trials support the efficacy of netarsudil ophthalmic solution for reducing elevated IOP in patients with OAG or OHT. The AC voted 9 yes/1 no that the efficacy benefits outweigh the identified safety risks.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION¹

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. The various types of glaucoma are distinguished by the causative physiological defect. It affects one person in 200 over the age of 40 and is the leading cause of irreversible blindness in the United States and worldwide. The global prevalence of open-angle glaucoma (OAG) between 40 and 80 years of age is estimated at 3.54%.² One of the primary risk factors is elevated IOP. The reduction and control of elevated IOP in OAG and ocular hypertension (OHT) is usually managed by chronic, long-term topical ocular therapy. When maximal tolerated medical therapy does not adequately control IOP, surgical therapy is the next option.

^b FDAAA factor (D): The expected or actual duration of treatment with the drug

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS³

Reduction of IOP is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. Multiple ophthalmic drug products are approved for lowering IOP in patients with OAG or OHT. These treatments include β -adrenergic receptor antagonists (β -blockers), α -adrenergic receptor agonists (α -agonists), parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs. Some of these treatments affect aqueous humor production (β -blockers, α -agonists, and CAIs), while others affect aqueous humor outflow (miotics, PGAs, and α -agonists). It is not uncommon for a patient with glaucoma to require more than one class of IOP-lowering products to control elevated IOP. Laser or surgical treatment may be recommended when medical therapy fails or is not tolerated. Netarsudil, if approved, would represent a new class of glaucoma treatment options that lower IOP by directly increasing trabecular outflow.

Table 1: FDA-Approved Drug Products Used for Lowering Elevated Intraocular Pressure

Pharmacologic Class/ Applicant	Trade Name	Established Name
Alpha-2 agonists		
Allergan, Inc.	Alphagan/Alphagan P	brimonidine tartrate
Alcon	Iopidine	apraclonidine
Beta-adrenergic antagonists		
Alcon	Betoptic/Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Bausch & Lomb	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharmaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	Brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan/ Travatan Z	travoprost
Merck	Zioptan	tafluprost
Alcon	Izba	travoprost
Bausch & Lomb	Vyzulta	latanoprostene bunod
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride

Alcon	Simbrinza	carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

Source: Wadhwa, S. Division of Transplant and Ophthalmology Products, Clinical Review of NDA 208254, November 8, 2017.

4 Benefit Assessment

Evidence of the effectiveness of netarsudil for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension (OHT) or open-angle glaucoma (OAG) was derived from three pivotal Phase 3 studies, Studies 301, 302, and 304. The three studies were similar in design: double-blind, randomized, multicenter, active-controlled, parallel-group comparison trials designed to confirm the IOP-lowering efficacy of netarsudil 0.02% ophthalmic solution dosed once daily (QD) in the evening (PM) over a 3-month period. For each of these studies, the primary efficacy endpoint was mean IOP measured at multiple time points at the Week 2, Week 6, and Month 3 visits.

Patients with OAG or OHT in both eyes and corrected visual acuity in each eye +1.0 logMAR^c or better were eligible for enrollment. The original Phase 3 protocols permitted enrollment of subjects 2 years of age or older, but only 2 subjects <18 years of age were enrolled in Study 302 and there were no subjects <18 years of age in the other pivotal studies. Subjects were not eligible if their glaucoma or OHT had a pseudoexfoliation or pigment dispersion component; if they had a history of angle closure or narrow angles; or if they had previous glaucoma intraocular surgery or glaucoma laser procedure in either eye. IOP following washout from prior IOP-lowering medications, if applicable, was required to be > 20 mmHg at 08:00 hours, and IOP > 17 mmHg at 10:00 and 16:00 hours. Additionally, IOP had to be < 27 mmHg in both eyes at all qualification time points.

All studies used timolol maleate 0.5% ophthalmic solution as the active comparator. All treatments were administered 1 drop to both eyes, and subjects in the QD PM groups received vehicle QD in the morning (AM) for masking. Studies were powered to show non-inferiority of netarsudil QD to timolol BID. The criteria for which were based on the upper limits of the 95% confidence intervals (CIs) for the treatment difference (netarsudil – timolol): within 1.5 mmHg for all 9 time points and within 1.0 mmHg for at least 5 (the majority) of the 9 time points.

Table 1: Netarsudil 0.02% Phase 3 Study Design

Study	Treatment	Baseline IOP
301 90-day safety and efficacy	Once-daily (PM) netarsudil 0.02% (n = 202) Twice-daily timolol (n = 209)	> 20 to < 27 mmHg

^c logarithm of the minimum angle of resolution, which is used by ophthalmologists, optometrists and vision scientists when evaluating visual acuity.

302 12-month safety, 3-month primary efficacy	Once-daily (PM) netarsudil 0.02% (n = 251) Twice-daily netarsudil 0.02% (n = 254) Twice-daily timolol (n = 251)	> 20 to < 27 mmHg
304 6-month safety, 3-month primary efficacy	Once-daily (PM) netarsudil 0.02% (n = 351) Twice-daily timolol (n = 357)	> 20 to < 30 mmHg

Additional safety data was considered from the Phase 3 study, OBS01, which is described below.

- **Study OBS01** was a prospective, targeted, multicenter, non-interventional, cohort study of 45 subjects at 10 sites who had ongoing corneal verticillata when they exited from Study 302. Study OBS01 had no set duration; the expectation was that subjects who consented would participate until their corneal verticillata in both eyes resolved or was stabilized, which was defined as no worsening of the corneal verticillata grading. Subjects were not treated with any investigational product in this observational study. They did, however, restart or continue treatment with IOP-lowering agents or other topical ocular medications, as recommended by their eye care provider.

Analysis Populations

The Intent-to-Treat (ITT) population was to include all randomized subjects who received at least 1 dose of study medication. The Per Protocol (PP) population was a subset of the ITT population and was to include subjects (and their visits) who did not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. This was to be the primary population for efficacy analyses and was to be used to summarize all efficacy variables.

Clinical Efficacy Results

In Study 301, the mean change in IOP at 08:00, 10:00, and 16:00 on Day 90 was 3.61, 3.36, and 3.30 mmHg in the netarsudil group and 4.90, 3.96, and 3.71 mmHg in the timolol group. According to the clinical reviewer, non-inferiority of QD netarsudil to BID timolol was not demonstrated in the PP population (baseline IOP <27 mmHg). The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 time points and within 1.0 mmHg at 4 of the 9 time points. Therefore, the pre-specified criteria for non-inferiority were not met.

In Study 302, the mean change in IOP at 08:00, 10:00, and 16:00 on Day 90 was 4.30, 4.26, and 3.30 mmHg, in the QD netarsudil group; 4.97, 4.33, and 4.05 mmHg, in the BID netarsudil group; and 5.07, 4.35, and 3.76 mmHg, in the timolol group. According to the clinical reviewer, non-inferiority of both QD and BID netarsudil to BID timolol was demonstrated in the PP population with maximum baseline IOP <25 mmHg in this study. Both netarsudil groups met the pre-specified criteria for non-inferiority compared to timolol.

In the PP population in Study 304, the mean change in IOP at 08:00, 10:00, and 16:00 on Day 90 was 4.54, 4.16, and 3.96 mmHg, respectively, in the netarsudil group and 5.15, 4.58, and 3.89 mmHg, respectively, in the timolol group. In the study's ITT population, the mean change in IOP at 08:00, 10:00,

and 16:00 on Day 90 was 4.43, 4.09, and 3.75 mmHg, in the netarsudil group and 5.16, 4.62, and 3.94 mmHg, in the timolol group. According to the clinical reviewer, netarsudil demonstrated non-inferiority to timolol in both the PP and ITT populations with maximum baseline IOP <25 mmHg in this study.

The clinical reviewer concluded that, overall, in subjects with a maximum baseline IOP <25 mmHg, netarsudil and timolol appeared to produce similar mean IOP reductions. The drug did not show non-inferiority to timolol for subjects with a maximum baseline IOP ≥25 mmHg. Based on the results of Studies 301, 302, and 304, the clinical reviewer concluded that the efficacy of QD netarsudil was equivalent to BID timolol in the subset of patients with IOP <25.

5 Risk Assessment & Safe-Use Conditions

Studies 301, 302, and 304 supported the clinical safety review and included 1058 subjects exposed to at least one dose of netarsudil 0.02% solution.

No drug-related systemic adverse events (AEs) were reported in the netarsudil clinical development program. Given the very low systemic exposure to netarsudil following ocular dosing, it is anticipated that drug-drug interactions will not be a concern in the intended patient population.

The most commonly reported AE was conjunctival hyperemia (53%), the majority of which was mild in nature. Other common ocular AEs reported at an incidence greater than 10% included corneal verticillata (20%), instillation site pain (20%), and conjunctival hemorrhage (17%). Instillation site pain and conjunctival hemorrhage are not uncommon AEs among other treatments for OAG or OHT; corneal verticillata, however, is unique.

5.1 DEATHS

Three deaths were reported during the netarsudil pivotal studies. One death was determined to be a result of acute leukemia and the other two were the result of acute myocardial infarction. All three events were judged not to be related to the test medication.

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Corneal Verticillata (CV)

Corneal verticillata (CV) was reported in 17% of the pooled safety population. This condition manifests as a whorl-like pattern of golden brown or gray deposits in the corneal epithelium in a clockwise fashion and is usually bilateral. CV develops secondary to intracellular phospholipid accumulation in the lysosomes. This sometimes results from concomitant treatment with a medication that binds with the cellular lipids of the corneal basal epithelial layer.^d

^d <https://www.aao.org/bcscsnippetdetail.aspx?id=27980840-6807-4c45-aaae-b8652b087987>, accessed October 24, 2017.

The cases of CV observed in netarsudil-treated patients were first noted at 4 weeks of once-daily dosing. According to the clinical reviewer, netarsudil is the first topical ophthalmic treatment with which CV was observed. To further investigate this finding, the Applicant conducted a special follow-up observational safety study, Study OBS01. At the completion of this study, CV had resolved in all subjects except for 3 whose CV remained stabilized, but unresolved. Of these 3 subjects (4 affected eyes), 2 subjects were taking a concomitant medication known to induce corneal epithelial changes (ibuprofen and naproxen, respectively). The 3 subjects whose CV remained unresolved did not have a clinically meaningful change in visual acuity. The clinical reviewer concluded that CV in the study subjects did not result in any apparent visual functional changes.

6 Expected Postmarket Use

Netarsudil is expected to be prescribed by ophthalmologists and used primarily by patients in an outpatient setting. The recommended dosage is one drop in the affected eye(s) once daily in the evening. Patients and their caregivers should be instructed to avoid allowing the dispensing container to contact the eye, in order to avoid bacterial contamination.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for netarsudil beyond routine pharmacovigilance and labeling. There are no recommended Post-Marketing Requirements (PMRs) or Phase 4 Commitments.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of netarsudil on the basis of the submitted efficacy and safety information.

The benefits of treatment with netarsudil were demonstrated by meeting the primary endpoints of the clinical trials. Based on these results, netarsudil was found to be efficacious with an acceptable safety profile for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Glaucoma is a life-long progressive disease that may lead to irreversible optic nerve damage and, eventually, vision loss. It is not uncommon for a patient with glaucoma to require more than one class of IOP-lowering products to control elevated IOP. If drug therapy fails or is not tolerated, patients may require laser or surgical treatment.

Netarsudil, if approved, would represent a new class of glaucoma treatment options, Rho kinase inhibitors. Although the risks associated with its use are not well-established, the most commonly reported AE was conjunctival hyperemia (53%), the majority of which was mild in nature. Additionally, netarsudil ophthalmic solution is associated with very low systemic absorption. No drug-related systemic AEs were reported in the netarsudil clinical development program and it is anticipated that drug-drug interactions will not be a concern in the intended patient population. The risks of netarsudil were discussed during an AC meeting. The AC voted 9-1 that the efficacy of netarsudil observed in the clinical trials outweighs its risks; the committee did not recommend a boxed warning, PMRs, or any additional risk mitigation measures beyond labeling.

The clinical reviewer concluded that netarsudil's risks can be managed with labeling and routine pharmacovigilance. Furthermore, they did not recommend a PMR or any Phase 4 Commitments.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable. Therefore, it is the opinion of this reviewer that a REMS is not necessary to ensure the benefits of netarsudil outweigh its risks. At the time of this review, labeling negotiation is ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should DTOP have any concerns or questions, or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

¹ Wadhwa, S. DTOP, Clinical Review of NDA 208254, November 8, 2017.

² McCann, P, Hogg, RE, Fallis, R, Azuara-Blanco, A. The effect of statins on intraocular pressure and on the incidence and progression of glaucoma: A systematic review and meta-analysis, statins and IOP, glaucoma incidence and progression. *Investigative ophthalmology & visual science*. 2016; 57(6), 2729-2748. Accessed October 24, 2017.

³ Wadhwa, S. DTOP, Clinical Review of NDA 208254, November 8, 2017.

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/s/

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12/18/2017

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