Brand Name: Rhopressa®

Generic Name: Netarsudil ophthalmic solution 0.02%.

Manufacturer: Aerie Pharmaceuticals- approved December 18, 2017.

Drug Class: Rho kinase inhibitor.

Uses:
- Labeled: Reduction of elevated IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).
- Unlabeled: None.

Mechanism of action: Exact mechanism unknown. Rhopressa may reduce IOP by increasing the outflow of aqueous humor through the trabecular meshwork.

Pharmacokinetics:
- Absorption: Systemic exposures were evaluated in 18 healthy subjects after topical ocular administration of RHOPRESSA 0.02% once daily (one drop bilaterally in the morning) for 8 days. There were no quantifiable plasma concentrations of netarsudil (lower limit of quantitation (LLOQ) 0.100 ng/mL) post dose on Day 1 and Day 8. Only one plasma concentration at 0.11 ng/mL for the active metabolite was observed for one subject on Day 8 at 8 hours post-dose.
- Metabolism: Metabolized by esterases in the eye to the active metabolite AR-13503.

Efficacy:
Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD. Double-masked, randomized, dose-response study of AR-13324 (netarsudil) versus latanoprost in patients with elevated intraocular pressure. Ophthalmology. 2015 Feb;122(2):302-7.
- Study design: Double-masked, randomized study in 22 private practice ophthalmology clinics. 224 patients were randomized and treated while 213 (95.1%) completed the study.
- Description of study: The objective of this 28-day study was to evaluate the ocular hypotensive efficacy and safety of netarsudil ophthalmic solution compared with a positive control, latanoprost ophthalmic solution, in patients with OAG or OHT. The primary efficacy endpoint was the mean diurnal IOP across subjects within the treatment group at day 28.
- Results: Netarsudil 0.01% and 0.02% dosed nightly produced large clinically and statistically significant reductions in IOP, with 0.02% producing slightly larger IOP reductions. Netarsudil 0.02% was less effective than latanoprost by ~1 mmHg in patients with unmedicated IOPs in the range of 22-35 mmHg. Netarsudil showed similar efficacy to latanoprost in a prespecified patient subgroup that excluded patients with baseline IOPs of >26 mmHg. The major safety finding was ocular hyperemia, which was more common for both concentrations of netarsudil than for latanoprost.
- Limitations: The 28-day duration of the study does not provide information on the long-term safety and efficacy of netarsudil. Also, the study did not enroll patients with a corneal thickness of >600 micrometers or in patients with forms of glaucomatous disease other than OAG.

- Conclusion: Netarsudil showed efficacy in reducing IOP in patients with OAG and OHT, however was slightly less effective than latanoprost in patients with higher baseline IOP. Netarsudil was generally well tolerated.

Serle JB, Katz LJ, McLaurin E, et al: Two Phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure. Am J Ophthalmol. 2018 Feb;186:116-127.

- Study design: Double-masked, randomized noninferiority clinical trials: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). A total of 1,167 patients were enrolled in the two studies. ROCKET-1 enrolled 756 patients while 595 completed the study. ROCKET-2 enrolled 411 patients while 367 completed the study.
- Description of study: The objective of this 28-day study was to evaluate the efficacy and ocular and systemic safety of netarsudil 0.02% ophthalmic solution in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT).
- Results: Treatment with netarsudil nightly produced clinically and statistically significant reductions from baseline IOP ($P < .001$), and was noninferior to timolol in the per-protocol population with maximum baseline IOP <25 mmHg in both studies. When baseline IOP was 25-30 mmHg, timolol provided significantly greater reductions in IOP compared with netarsudil. There were no netarsudil-related systemic safety issues in these studies, in which patients were exposed to netarsudil for up to 3 months.
- Limitations: The study excluded, without definition, individuals with clinically significant ocular disease in either eye or with systemic disease that might interfere with the study.
- Conclusion: Netarsudil 0.02% was found to be effective and well tolerated for the treatment of patients with OAG and OHT in patients with a baseline IOP <25 mmHg.

Contraindications: No contraindications listed in the manufacturer's labeling.

Precautions: Avoid touching the dropper tip with fingers, eyes, eyelids, or surrounding areas to minimize contamination of the dropper tip. Inadvertent contamination of multiple-dose ophthalmic solutions has caused bacterial keratitis.

Adverse effects:

>10%:

- Local: Application site pain (20%)
- Ophthalmic: Conjunctival hyperemia (53%), conjunctival hemorrhage (20%), corneal verticillata disease (20%)

1-10%:

- Dermatologic: Eyelid erythema (5-10%)
- Local: Application site erythema (5-10%)
- Ophthalmic: Blurred vision (5-10%), corneal pigmentation/staining (5-10%), decreased visual acuity (5-10%), increased lacrimation (5-10%)

Drug Interactions: There are no known significant interactions.

Dosing/Administration:

- Adult- Instill 1 drop into affected eye(s) once daily in the evening (Maximum: 1 drop once daily)
- Geriatric- Refer to adult dosing.
- Pediatric- Safety and efficacy have not been established in patients younger than 18 years.
- Renal impairment- No dosage adjustments provided in the manufacturer's labeling; dosage adjustments are unlikely due to low systemic absorption.
- Hepatic impairment- No dosage adjustments provided in the manufacturer's labeling; dosage adjustments are unlikely due to low systemic absorption.

Use in special circumstances:

- Contact lens wearers- Contains benzalkonium chloride, which may be absorbed by soft contact lenses. Remove contact lens prior to instillation; may reinsert 15 minutes following administration.
- May be used with other eye drops to lower intraocular pressure. If using more than one ophthalmic product, wait at least 5 minutes in between application of each medication.

Conclusion: Netarsudil is a topical ophthalmic solution dosed once nightly with a novel mechanism to lower IOP. The ocular hypotensive efficacy of netarsudil, when compared to latanoprost and timolol, may be less in patients with higher baseline IOP. Netarsudil has once daily dosing, which does provide an advantage over other ocular hypotensives that may require dosing multiple times daily. Due to price, netarsudil should be considered in patients who do not have an adequate response to traditional ocular hypotensives. Because of the unique mechanism of action, additional studies should focus on the potential additive efficacy when combining netarsudil with other agents (latanoprost, timolol) to further lower IOP in patients not responding fully to other available agents.

References:

1. Product Information: Rhopressa® ophthalmic solution, netarsudil ophthalmic solution. Aerie Pharmaceuticals Inc (per FDA), Irvine, CA, 2017.
2. Serle JB, Katz LJ, McLaurin E, et al: Two Phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure. Am J Ophthalmol. 2018 Feb;186:116-127. Accessed April 9, 2018.
3. Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD. Double-masked, randomized, dose-response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. Ophthalmology. 2015 Feb;122(2):302-7. Accessed April 9, 2018.
4. Netarsudil. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed April 9, 2018.

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