RHOPRESSA- netarsudil solution/ drops
Alcon Laboratories, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RHOPRESSA® safely and effectively. See full prescribing information for RHOPRESSA®.
RHOPRESSA® (netarsudil ophthalmic solution) 0.02%, for topical ophthalmic use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

DOSAGE AND ADMINISTRATION

One drop into the affected eye(s) once daily in the evening. (2)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 0.2 mg/mL of netarsudil. (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

The most common adverse reaction is conjunctival hyperemia (53%). Other common adverse reactions, approximately 20% include: corneal verticillata, instillation site pain, and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aerie Pharmaceuticals, Inc. at 1-855-740-1924, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RHOPRESSA (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart *[see Patient Counseling Information (17)].*

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 0.2 mg/mL of netarsudil.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface [see *Patient Counseling Information (17)].*

5.2 Use with Contact Lenses

Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Six percent of patients discontinued therapy due to conjunctival hyperemia. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata

Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on RHOPRESSA use 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]*.

Data

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}).

8.2 Lactation

Risk Summary

There are no data on the presence of RHOPRESSA 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 *[see Clinical Pharmacology (12.3)]*, 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 RHOPRESSA and any potential adverse effects on the breast-fed child from RHOPRESSA.

8.4 Pediatric Use

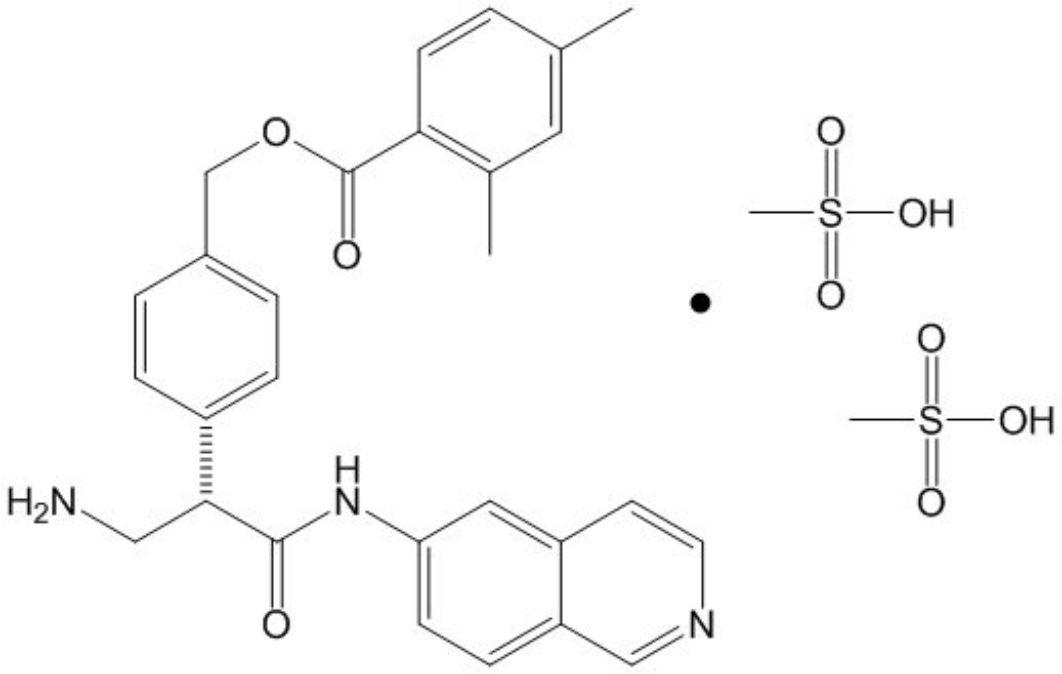
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

11 DESCRIPTION

Netarsudil is a Rho kinase inhibitor. Its chemical name is (S)-4-(3-amino-1-(isoquinolin-6-yl-amino)-1-oxopropan-2-yl) benzyl 2,4-dimethylbenzoate dimesylate. The molecular formula of the free base is $C_{28}H_{27}N_3O_3$ and the molecular formula of the dimesylate is $C_{30}H_{35}N_3O_9S_2$. The molecular weight of the free base is 453.54 and the molecular weight of the dimesylate is 645.74. The chemical structure is:



Netarsudil dimesylate is a light yellow-to-white powder that is freely soluble in water,

soluble in methanol, sparingly soluble in dimethyl formamide, and practically insoluble in dichloromethane and heptane.

RHOPRESSA (netarsudil ophthalmic solution) 0.02% is supplied as a sterile, isotonic, buffered aqueous solution of netarsudil dimesylate with a pH of approximately 5 and an osmolality of approximately 295 mOsmol/kg. It is intended for topical application in the eye. Each mL of RHOPRESSA contains 0.2 mg of netarsudil (equivalent to 0.28 mg of netarsudil dimesylate). Benzalkonium chloride, 0.015%, is added as a preservative. The inactive ingredients are: boric acid, mannitol, sodium hydroxide to adjust pH, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Netarsudil is a rho kinase inhibitor, which is believed to reduce IOP by increasing the outflow of aqueous humor through the trabecular meshwork. The exact mechanism is unknown.

12.3 Pharmacokinetics

Absorption

The systemic exposures of netarsudil and its active metabolite, AR-13503, 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

After topical ocular dosing, netarsudil is metabolized by esterases in the eye.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

14 CLINICAL STUDIES

RHOPRESSA 0.02% was evaluated in three randomized and controlled clinical trials, namely AR-13324-CS301 (NCT 02207491, referred to as Study 301), AR-13324-CS302 (NCT 02207621, referred to as Study 302), and AR-13324-CS304 (NCT 02558374, referred to as Study 304), in patients with open-angle glaucoma or ocular hypertension. Studies 301 and 302 enrolled subjects with baseline IOP lower than 27 mmHg and Study 304 enrolled subjects with baseline IOP lower than 30 mmHg. The treatment duration

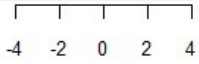
was 3 months in Study 301, 12 months in Study 302, and 6 months in Study 304.

The three studies demonstrated up to 5 mmHg reductions in IOP for subjects treated with RHOPRESSA 0.02% once daily in the evening. For patients with baseline IOP < 25 mmHg, the IOP reductions with RHOPRESSA 0.02% dosed once daily were similar to those with timolol 0.5% dosed twice daily (see Table 1). For patients with baseline IOP equal to or above 25 mmHg, however, RHOPRESSA 0.02% resulted in smaller mean IOP reductions at the morning time points than timolol 0.5% for study visits on Days 43 and 90; the difference in mean IOP reduction between the two treatment groups was as high as 3 mmHg, favoring timolol.

Table 1: Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time

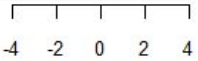
Study 301: Subjects with Baseline IOP < 25 mmHg

Visit	Rhopressa (N=113)	Timolol (N=124)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	22.4	22.5	
10am	21.3	21.1	
4pm	20.6	20.5	
Change From Baseline			
Day 15			
8am	-5.1	-4.7	-0.3 (-0.9, 0.3)
10am	-5.0	-4.2	-0.9 (-1.5, -0.3)
4pm	-4.4	-3.4	-0.9 (-1.6, -0.3)
Day 43			
8am	-4.5	-4.7	0.2 (-0.5, 0.9)
10am	-4.3	-4.2	-0.2 (-0.8, 0.5)
4pm	-4.0	-3.3	-0.7 (-1.4, 0.0)
Day 90			
8am	-4.2	-4.6	0.4 (-0.2, 1.1)
10am	-3.9	-3.7	-0.2 (-0.9, 0.5)
4pm	-3.6	-3.2	-0.4 (-1.0, 0.3)



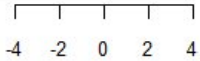
Study 301: Subjects with Baseline IOP >= 25 and < 27 mmHg

Visit	Rhopressa (N=69)	Timolol (N=64)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	25.1	25.1	
10am	23.9	23.6	
4pm	23.7	23.3	
Change From Baseline			
Day 15			
8am	-4.3	-5.7	1.3 (0.4, 2.3)
10am	-4.9	-5.0	0.1 (-0.9, 1.2)
4pm	-4.7	-4.6	-0.1 (-1.2, 0.9)
Day 43			
8am	-3.3	-6.0	2.7 (1.5, 3.8)
10am	-3.7	-5.3	1.6 (0.4, 2.7)
4pm	-3.7	-4.8	1.2 (0.0, 2.3)
Day 90			
8am	-2.6	-5.5	3.0 (1.8, 4.1)
10am	-2.2	-4.7	2.5 (1.4, 3.6)
4pm	-2.6	-4.9	2.3 (1.2, 3.5)



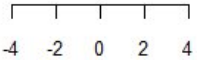
Study 302: Subjects with Baseline IOP < 25 mmHg

Visit	Rhopressa (N=129)	Timolol (N=142)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	22.5	22.5	
10am	21.3	21.3	
4pm	20.4	20.7	
Change From Baseline			
Day 15			
8am	-4.5	-4.9	0.4 (-0.2, 1.0)
10am	-4.6	-4.4	-0.2 (-0.8, 0.4)
4pm	-3.9	-3.8	-0.1 (-0.6, 0.5)
Day 43			
8am	-4.6	-5.1	0.5 (-0.1, 1.1)
10am	-4.4	-4.7	0.3 (-0.3, 0.9)
4pm	-3.5	-4.0	0.5 (-0.1, 1.1)
Day 90			
8am	-4.3	-5.1	0.8 (0.1, 1.5)
10am	-4.3	-4.4	0.1 (-0.5, 0.8)
4pm	-3.4	-3.7	0.3 (-0.4, 1.0)



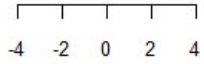
Study 302: Subjects with Baseline IOP >= 25 and < 27 mmHg

Visit	Rhopressa (N=77)	Timolol (N=75)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	25.1	25.2	
10am	24.0	23.9	
4pm	23.5	23.3	
Change From Baseline			
Day 15			
8am	-4.5	-5.9	1.4 (0.5, 2.3)
10am	-4.5	-5.4	0.9 (-0.1, 1.9)
4pm	-4.9	-4.3	-0.6 (-1.5, 0.3)
Day 43			
8am	-3.4	-5.9	2.6 (1.5, 3.7)
10am	-3.8	-5.3	1.5 (0.5, 2.6)
4pm	-3.9	-4.9	0.9 (0.0, 1.9)
Day 90			
8am	-3.4	-5.6	2.1 (1.1, 3.2)
10am	-3.5	-5.3	1.7 (0.6, 2.8)
4pm	-4.4	-4.3	-0.1 (-1.2, 1.0)



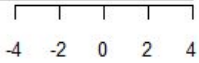
Study 304: Subjects with Baseline IOP < 25 mmHg

Visit	Rhopressa (N=186)	Timolol (N=187)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	22.4	22.4	
10am	21.1	21.3	
4pm	20.7	20.7	
Change From Baseline			
Day 15			
8am	-4.7	-4.9	0.2 (-0.4, 0.8)
10am	-4.5	-4.5	0.0 (-0.5, 0.5)
4pm	-4.4	-3.8	-0.6 (-1.1, -0.1)
Day 43			
8am	-4.6	-4.8	0.3 (-0.3, 0.8)
10am	-4.3	-4.3	-0.1 (-0.6, 0.5)
4pm	-4.1	-4.0	-0.1 (-0.6, 0.4)
Day 90			
8am	-4.5	-5.2	0.6 (0.0, 1.2)
10am	-4.1	-4.5	0.4 (-0.2, 0.9)
4pm	-3.9	-3.9	0.0 (-0.6, 0.5)



Study 304: Subjects with Baseline IOP >= 25 and < 30 mmHg

Visit	Rhopressa (N=120)	Timolol (N=130)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	26.3	26.0	
10am	25.2	24.9	
4pm	24.5	24.0	
Change From Baseline			
Day 15			
8am	-4.7	-5.9	1.2 (0.3, 2.0)
10am	-5.0	-5.6	0.6 (-0.2, 1.5)
4pm	-4.3	-4.9	0.6 (-0.2, 1.3)
Day 43			
8am	-4.3	-6.2	1.9 (1.0, 2.8)
10am	-4.7	-5.8	1.1 (0.2, 1.9)
4pm	-4.3	-4.4	0.2 (-0.6, 1.0)
Day 90			
8am	-4.5	-6.1	1.6 (0.6, 2.5)
10am	-4.1	-5.9	1.8 (0.9, 2.7)
4pm	-3.9	-5.0	1.1 (0.2, 1.9)



This table was produced based on the observed data from all randomized subjects who did not have major protocol violations. The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol BID 0.5% were based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP.

16 HOW SUPPLIED/STORAGE AND HANDLING

RHOPRESSA® (netarsudil ophthalmic solution) 0.02% (0.2 mg per mL) is supplied sterile in opaque white low density polyethylene bottles and tips with white polypropylene caps.

2.5 mL fill in a 4 mL container
NDC # 70727-497-25

Storage: Store at 2°C to 8°C (36°F to 46°F) until opened. After opening, the product may be kept at 2°C to 25°C (36°F to 77°F) for up to 6 weeks. If after opening the product is kept refrigerated at 2°C to 8°C (36°F to 46°F), then the product can be used until the expiration date stamped on the bottle. During shipment, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 14 days.

17 PATIENT COUNSELING INFORMATION

Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions (5.1)].*

When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician’s advice concerning the continued use of RHOPRESSA.

Use with Contact Lenses

Advise patients that RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs

Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes between applications.

Missed Dose

Advise patients that if one dose is missed, treatment should continue with the next dose in the evening.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043; 9,931,336

RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 70727-497-25

rhopressa®
(netarsudil ophthalmic solution) 0.02%

For topical application in the eye

Sterile
Rx only

2.5 mL

Usual dosage:
One drop in the affected eye(s) once daily in the evening.

Each mL Rhopressa®
ophthalmic solution contains:
Active: netarsudil mesylate 0.285 mg

Preservative:
benzalkonium chloride 0.15 mg

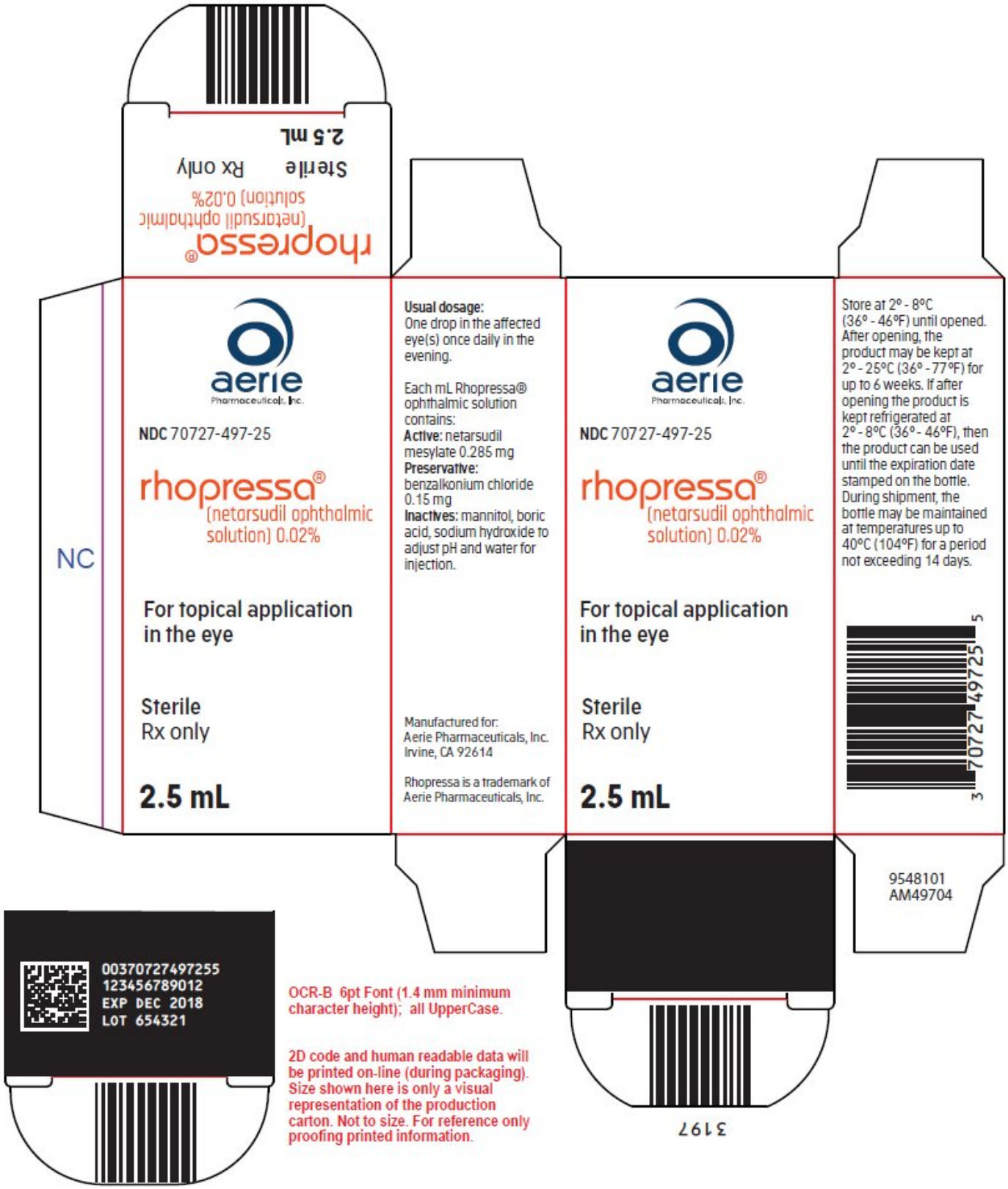
Inactives: mannitol, boric

acid, sodium hydroxide to
adjust pH and water for injection.

Manufactured for:
Aerie Pharmaceuticals, Inc.
Irvine, CA 92614

Rhopressa is a trademark of
Aerie Pharmaceuticals, Inc.

Store at 2° - 8°C
(36° - 46°F) until opened.
After opening the,
product may be kept at



NDC 70727-497-25

rhopressa®

(netarsudil ophthalmic solution) 0.02%

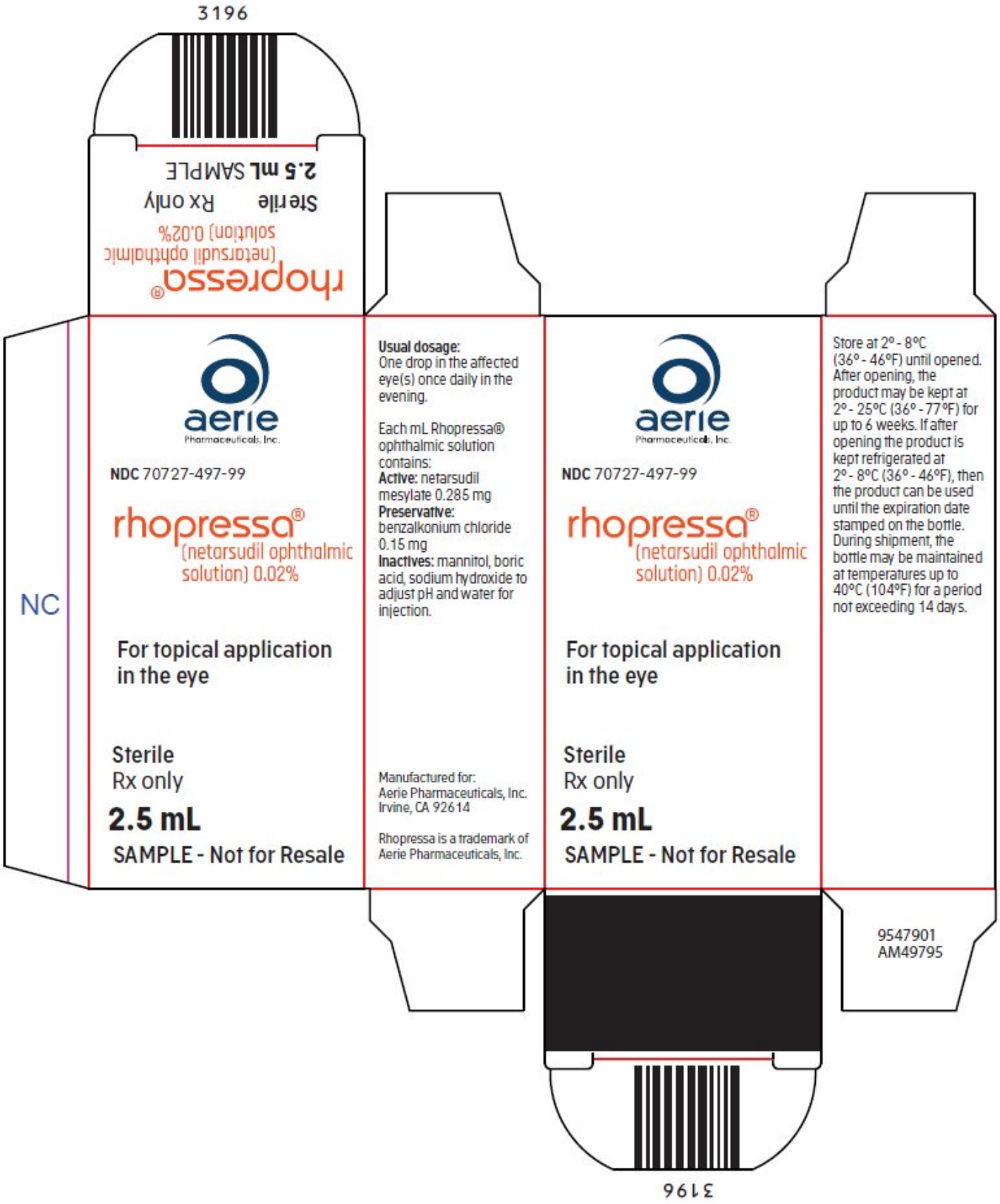
For topical application in the eye

Sterile

Rx only

2.5 mL

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL



NDC 70727-497-99

rhopressa®

(netarsudil ophthalmic solution) 0.02%

For topical application in the eye

Sterile

Rx only

2.5 mL

SAMPLE – Not for Resale

RHOPRESSA

netarsudil solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70727-497
Route of Administration	OPHTHALMIC, TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NETARSUDIL MESYLATE (UNII: VL756B1K0U) (NETARSUDIL - UNII:W6I5QDT7QI)	NETARSUDIL	0.200 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
MANNITOL (UNII: 3OWL53L36A)	
BORIC ACID (UNII: R57ZHV85D4)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:70727-497-25	1 in 1 CARTON	12/18/2017	
1		2.5 mL in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:70727-497-99	1 in 1 CARTON	12/18/2017	
2		2.5 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208254	12/18/2017	

Labeler - Alcon Laboratories, Inc. (008018525)

Revised: 2/2023 Alcon Laboratories, Inc.