Summary Report of Benefit-Risk Assessment

RHOPRESSA OPHTHALMIC SOLUTION, 0.02% w/v

NEW DRUG APPLICATION

Active Ingredient(s)	Netarsudil mesylate
Product Registrant	Santen Pharmaceutical Asia Pte. Ltd.
Product Registration Number	SIN16816P
Application Route	Abridged evaluation
Date of Approval	4 July 2023

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A INTRODUCTION

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

The active substance, netarsudil, is a Rho kinase inhibitor, which is believed to reduce IOP by increasing the outflow of aqueous humour through the trabecular meshwork.

Each ml of Rhopressa contains 0.2 mg of netarsudil (equivalent to 0.28 mg of netarsudil mesylate). 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.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, netarsudil mesylate, is manufactured at Regis Technologies Inc, Morton Grove, USA. The drug product, Rhopressa ophthalmic solution 0.02% w/v, is manufactured at Aerie Pharmaceuticals Ireland Limited, Westmeath, Ireland.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at -20^{o}C ± 5^{o}C with a re-test period of 48 months. The packaging is an amber, Type III glass bottle with polytetrafluoroethylene (PTFE) lined screw top closure packed into foil/polyethylene/mylar pouch containing silica gel desiccant packs.

Drug product:

The manufacturing process involves formulation followed by prefiltration, sterile filtration and aseptic filling. This is considered to be a standard manufacturing process.

The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored between 2ºC and 8ºC. The in-use period after opening is one month, as supported by in-use stability data. The container closure system is a white low-density polyethylene bottle with linear low-density polyethylene tip and a polypropylene cap containing 2.5 ml of solution.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of netarsudil ophthalmic solution for the reduction of elevated IOP in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) comprised data from three pivotal Phase III studies, AR-13324-CS301 (ROCKET 1), AR-13324-CS302 (ROCKET 2) and AR-13324-CS304 (ROCKET 4). The three studies were of similar design, with key differences in the upper limit of baseline IOP, baseline IOP of the primary endpoint population and study duration.

The application was further supported by three randomised, double-blinded Phase II studies, AR-13324-CS201 (Study 201), AR-13324-CS202 (Study 202) and AR-13324-CS204 (Study 204). Studies 201 and 202 were conducted to evaluate the dose-response and dosing regimen of netarsudil, while Study 204 was conducted to evaluate the efficacy of netarsudil during nocturnal and diurnal periods.

Overview of efficacy studies

Study number	Study design	Treatments	Primary endpoint
Pivotal studies			
AR-13324-CS301 (ROCKET 1)	Phase III, randomised, double-blind, multicentre, 3-month study of netarsudil vs timolol in patients with OAG or OHT in both eyes, and with unmedicated 08:00 hour IOP > 20 mmHg and < 27 mmHg in the study eye (N=411).	Netarsudil 0.02% once daily Timolol maleate 0.5% twice daily Treatment duration: 3 months	Mean IOP at 08:00, 10:00, and 16:00 hours on Day 15, Day 43 and Day 90
AR-13324-CS302 (ROCKET 2)	Phase III, randomised, double-blind, multicentre, 12-month study of netarsudil vs timolol in patients with OAG or OHT in both eyes, and with unmedicated 08:00 hour IOP > 20 mmHg and < 27 mmHg in the study eye (N=756).	Netarsudil 0.02% once daily Netarsudil 0.02% twice daily Timolol maleate 0.5% twice daily Treatment duration: 12 months	Mean IOP at 08:00, 10:00, and 16:00 hours on Day 15, Day 43 and Day 90 of subjects with maximum baseline IOP < 25 mmHg
AR-13324-CS304 (ROCKET 4)	Phase III, randomised, double-blind, multicentre, 6-month study of netarsudil vs timolol in patients with OAG or OHT in both eyes,	Netarsudil 0.02% once daily	Mean IOP at 08:00, 10:00, and 16:00 hours on Day 15, Day 43 and Day 90

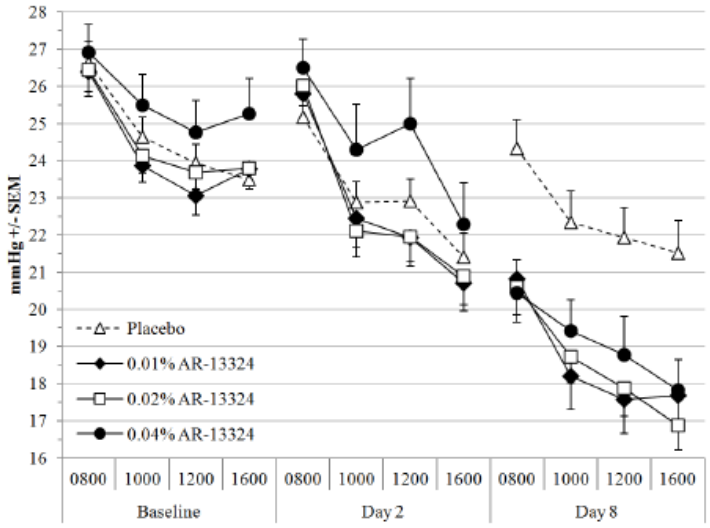
	and with unmedicated 08:00 hour IOP > 20 mmHg and < 30 mmHg in the study eye (N=708).	Timolol maleate 0.5% twice daily Treatment duration: 6 months	of subjects with maximum baseline IOP < 25 mmHg
Supportive studies			
AR-13324-CS201 (Study 201)	Phase IIa, randomised, double-blind, multicentre, 7-day study of netarsudil vs placebo in patients with OAG or OHT in one or both eyes and with unmedicated IOP ≥ 24 mmHg at 08:00 hours (N=85)	Netarsudil 0.01% once daily Netarsudil 0.02% once daily Netarsudil 0.04% once daily Vehicle once daily Treatment duration: 7 days	Mean IOP at 08:00, 10:00, 12:00 and 16:00 hours on Day 8
AR-13324-CS202 (Study 202)	Phase IIb, randomised, double-blind, multicentre, 28-day study of netarsudil vs latanoprost in patients with OAG or OHT in one or both eyes and with unmedicated IOP ≥ 24 mmHg at 08:00 hours (N=224)	Netarsudil 0.01% once daily Netarsudil 0.02% once daily Latanoprost 0.005% once daily Treatment duration: 28 days	Mean diurnal IOP at Day 28
AR-13324-CS204 (Study 204)	Phase II, randomised, double-blind, single centre, 7-day study of netarsudil vs placebo in patients with OAG or OHT in both eyes and with unmedicated IOP > 17 mmHg in one or both eyes and < 30 mmHg in both eyes between 12:00 and 16:00 hours (N=12)	Netarsudil 0.02% once daily Vehicle once daily Treatment duration: 7 days	Mean change from baseline in the mean nocturnal IOP (defined as the mean of 4 nocturnal time points at 21:00, 00:00, 03:00, and 06:00 hours) at Day 8/9

Study 201

Study 201 was a 7-day Phase IIa study in 85 subjects with open-angle glaucoma (OAG) or OHT, comparing three dose strengths of netarsudil (0.04%, 0.02% and 0.01%) with placebo dosed once daily at 08:00 hours. The primary efficacy endpoint was the mean IOP at 08:00, 10:00, 12:00, and 16:00 hours on Day 8. The largest reductions in mean IOP in the study were achieved by the netarsudil 0.02% and 0.04% concentrations at 16:00 hours on Day 8, approximately 8 hours following administration of the morning dose. At 16:00 hours, mean IOP change from baseline were -6.1 mmHg, -6.9 mmHg, -7.2 mmHg, and -1.8 mmHg for netarsudil 0.01%, 0.02%, 0.04%, and vehicle, respectively. Mean change from baseline at Day 8 was

greater for netarsudil 0.02% and 0.04% than netarsudil 0.01% at most time points (Figure 1). Adverse events occurred in 59%, 76%, 90% and 13% of subjects in the netarsudil 0.01%, 0.02%, 0.04% and vehicle groups, respectively. The data suggested that the top of the dose response curve was reached at 0.02% dosed once a day.

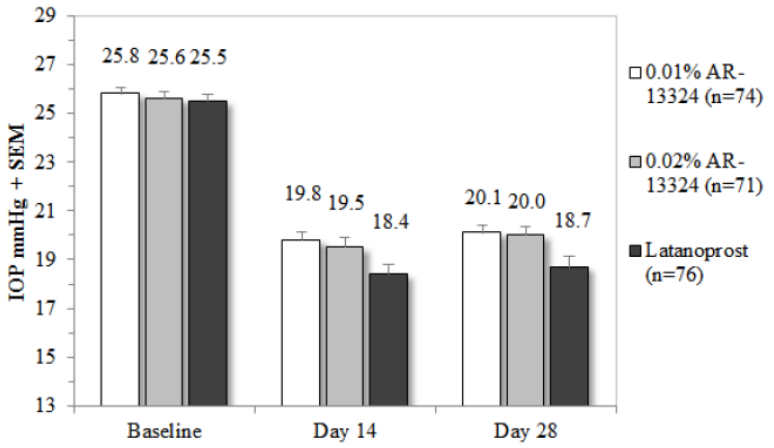
Figure 1 Study AR-13324-CS201: Dose Response for AR-13324 Ophthalmic Solution Dosed QD AM (mITT Population)



Study 202

Study 202 was a 28-day Phase IIb non-inferiority study in 224 subjects with OAG or OHT, comparing netarsudil 0.02% and 0.01% to latanoprost 0.005% dosed once daily in the evening (PM). The primary efficacy endpoint was the mean diurnal IOP at Day 28. Neither netarsudil strengths demonstrated non-inferiority to latanoprost as the null hypothesis of at least a 1.5 mmHg difference between netarsudil and latanoprost was not rejected (95% upper confidence interval (CI) of 2.3 and 2.2 at Day 28, with netarsudil 0.01% and 0.02%, respectively). Compared to netarsudil 0.01%, netarsudil 0.02% showed marginally greater reduction in mean diurnal IOP at Day 28 and marginally greater reduction in mean IOP at 2 of 3 time points on Day 28 (Figure 2).

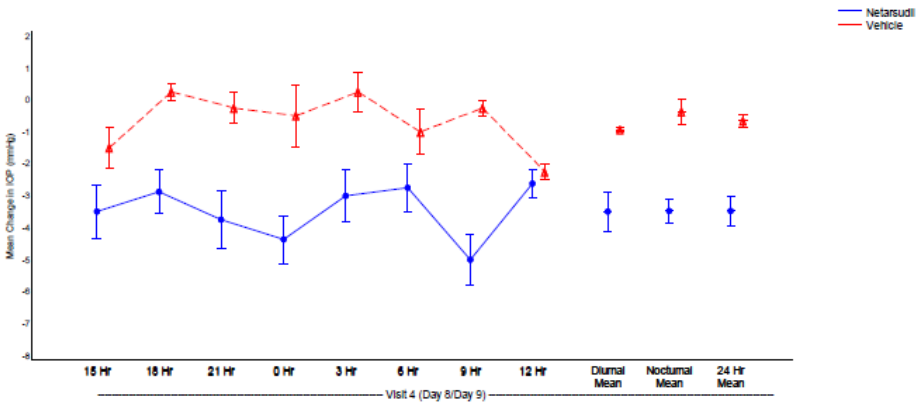
Figure 2 Study AR-13324-CS202: Mean Diurnal IOP for AR-13324 Ophthalmic Solution 0.01% and 0.02% Dosed QD PM (mITT Population)



Study 204

Study 204 was a placebo-controlled Phase II study in 12 subjects with OAG or OHT, evaluating the ocular hypotensive efficacy of netarsudil 0.02% dosed once daily in the evening for 7 days. The primary efficacy endpoint was the mean change from baseline in the mean nocturnal IOP (defined as the mean of 4 nocturnal time points at 21:00, 00:00, 03:00, and 06:00 hours) at Day 8/9. Netarsudil 0.02% demonstrated a statistically significant mean change from baseline of -3.5 mmHg in nocturnal (21:00 to 06:00 hours) IOP at Day 8/9 ($p < 0.0001$). The mean change from baseline in diurnal IOP (09:00 to 18:00 hours) was also -3.5 mmHg. In contrast, the mean change from baseline in the vehicle group was -0.4 mmHg (nocturnal period) and -0.9 mmHg (diurnal period) (Figure 3).

Figure 3 **Mean change from Baseline in mean IOP, mean diurnal IOP, mean nocturnal IOP, and mean 24-hour IOP: Netarsudil- vs. Vehicle- (Study Eye, ITT population)**



Study ROCKET 1

Study ROCKET 1 was a Phase III, randomised, double-blind, multicentre, 3-month study comparing netarsudil with timolol maleate in patients with OAG or OHT in both eyes, and with unmedicated 08:00 hour IOP > 20 mmHg and < 27 mmHg in the study eye.

Patients in the study were randomised in a 1:1 ratio to receive netarsudil 0.02% once daily in the evening or timolol maleate 0.5% twice daily for 3 months. As an approved treatment option for IOP reduction in OAG and OHT, the use of timolol as an active comparator was considered acceptable.

The primary efficacy endpoint was mean IOP at 08:00, 10:00, and 16:00 hours on Day 15, Day 43 and Day 90. To demonstrate non-inferiority of netarsudil to timolol, the upper limit of the 95% CI for the difference (netarsudil – timolol) in mean IOP values must be within 1.5 mmHg at all 9 time points (08:00, 10:00, and 16:00 hours on Day 15, Day 43, and Day 90) and within 1.0 mmHg at minimally 5 of 9 time points. The non-inferiority design and non-inferiority margin were considered appropriate. The primary analysis of the primary endpoint was conducted on the Per Protocol (PP) population, which comprised all randomised subjects who received at least one dose of study drug and who did not have major protocol violations. The analysis was also conducted on the Intent-to-Treat (ITT) population (i.e., all randomised subjects who received at least one dose of study drug) as a secondary analysis. Key secondary efficacy endpoints included mean change from baseline IOP at each post-treatment time point, mean percent change from diurnally adjusted baseline IOP at each time point, and mean diurnal IOP at each post-treatment visit.

A total of 411 patients were randomised in the study: 202 patients in the netarsudil arm and 209 patients in the timolol arm. The demographic and baseline characteristics of subjects were generally well-balanced across treatment groups. The mean age was 65.0 years (range 20 to 96 years), the majority of subjects were female (61%), White (75.4%), and 1.5% of subjects were Asian. Study eye diagnosis was OAG for 65.7% and OHT for 34.3% of the enrolled patients. Use of prostaglandin analogues (PGAs) was reported for 51.6% of subjects. The only other ocular medication used by more than 10% of subjects was timolol (14.4%). Mean IOP at screening was 20.0 and 19.4 mmHg in the netarsudil and timolol arms, respectively.

The primary analysis of difference in mean IOP did not demonstrate non-inferiority of netarsudil to timolol in the overall PP population (baseline IOP < 27 mmHg) (Table 1) and in the ITT population. The upper 95% CI for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 timepoints and within 1.0 mmHg at 4 of 9 timepoints in the PP population, therefore it did not meet the pre-specified criteria for non-inferiority. In the ITT population, the upper 95% CI for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 timepoints and within 1.0 mmHg at 3 of 9 timepoints.

A post-hoc analysis performed in the PP population with baseline IOP < 25 mmHg demonstrated non-inferiority of netarsudil to timolol (Table 2). The upper 95% CI for differences in mean IOP was within 1.5 mmHg at all 9 timepoints and within 1.00 mmHg at 8 of 9 timepoints. In patients with baseline IOP ≥ 25 mmHg and < 27 mmHg, netarsudil demonstrated reductions in IOP at all timepoints, but non-inferiority to timolol was not demonstrated (Table 3).

At each post-baseline visit, the mean percent reduction from baseline IOP in the PP population ranged from 14.98% to 22.49% in the netarsudil group and 16.66% to 21.80% in the timolol group (Table 4). The mean diurnal IOPs at Days 15, 43, and 90 were 17.72, 18.45, and 19.06 mmHg in the netarsudil group, respectively, and 17.86, 17.80, and 18.06 mmHg in the timolol group. The mean changes from baseline for mean diurnal IOP at Days 15, 43, and 90 were -4.81, -4.06, and -3.41, mmHg in the netarsudil group, and -4.41, -4.46, and -4.22 mmHg in the timolol group, respectively, which were all statistically significant ($p<0.0001$). The difference in mean diurnal IOP between treatment groups was not statistically significant at Day 15 ($p=0.079$) or Day 43 ($p=0.131$), but was statistically significant at Day 90 ($p=0.002$) favouring the timolol group.

Table 1 [ROCKET 1]: Study eye IOP (mmHg) by Visit (PP Population with observed data-baseline IOP < 27)

Day and Time	Mean IOP Netarsudil N=182	Mean IOP Timolol N=188	Mean difference (95% CI) Netarsudil - Timolol
Baseline			
08:00	23.42	23.37	
10:00	22.28	21.92	
16:00	21.78	21.45	
Day 15			
08:00	18.68	18.33	0.35 (-0.27, 0.96)
10:00	17.29	17.55	-0.26 (-0.87, 0.36)
16:00	17.24	17.70	-0.45 (-1.08, 0.17)
Day 43			
08:00	19.35	18.24	1.11 (0.42, 1.80)
10:00	18.14	17.44	0.70 (0.04, 1.36)
16:00	17.86	17.71	0.15 (-0.52, 0.83)

Day 90			
08:00	19.81	18.47	1.33 (0.64, 2.03)
10:00	18.92	17.96	0.96 (0.26, 1.66)
16:00	18.48	17.74	0.74 (0.07, 1.42)

Table 2 [ROCKET 1]: Study eye IOP (mmHg) by Visit (PP Population with observed data-baseline IOP < 25) (post-hoc analysis)

Day and Time	Mean IOP Netarsudil N=113	Mean IOP Timolol N=124	Mean difference (95% CI) Netarsudil - Timolol
Baseline			
08:00	22.39	22.50	
10:00	21.28	21.07	
16:00	20.62	20.52	
Day 15			
08:00	17.34	17.78	-0.44 (-1.10, 0.22)
10:00	16.18	16.98	-0.81 (-1.44, -0.17)
16:00	16.22	17.14	-0.92 (-1.58, -0.26)
Day 43			
08:00	17.85	17.81	0.05 (-0.68, 0.77)
10:00	16.88	16.96	-0.08 (-0.74, 0.58)
16:00	16.57	17.26	-0.69 (-1.40, 0.02)
Day 90			
08:00	18.22	17.91	0.31 (-0.40, 1.02)
10:00	17.34	17.43	-0.09 (-0.82, 0.63)
16:00	17.02	17.37	-0.35 (-1.03, 0.34)

Table 3 [ROCKET 1]: Study eye IOP (mmHg) by Visit (PP Population with observed data-baseline IOP ≥ 25 and < 27) (post-hoc analysis)

Day and Time	Mean IOP Netarsudil N=69	Mean IOP Timolol N=64	Mean difference (95% CI) Netarsudil - Timolol
Baseline			
08:00	25.11	25.05	
10:00	23.92	23.58	
16:00	23.68	23.25	
Day 15			
08:00	20.78	19.41	1.38 (0.36, 2.39)
10:00	19.01	18.62	0.40 (-0.70, 1.49)
16:00	18.82	18.75	0.07 (-1.04, 1.18)
Day 43			
08:00	21.78	19.09	2.69 (1.53, 3.84)
10:00	20.17	18.37	1.80 (0.60, 3.00)
16:00	19.95	18.56	1.39 (0.18, 2.60)
Day 90			
08:00	22.52	19.56	2.96 (1.83, 4.09)
10:00	21.58	18.98	2.59 (1.48, 3.71)
16:00	20.93	18.46	2.47 (1.32, 3.63)

Table 4 [ROCKET 1]: Mean Percent Change from Diurnally Adjusted Baseline in Study Eye IOP by Visit (PP Population with observed data)

Day and Time	Mean percent change in IOP Netarsudil N=182	Mean percent change in IOP Timolol N=188	Mean difference (95% CI) Netarsudil - Timolol
Day 15			
08:00	-20.53	-21.50	0.97 (-1.27, 3.20)

10:00	-22.49	-19.77	-2.72 (-5.21, -0.22)
16:00	-20.83	-17.04	-3.79 (-6.53, -1.05)
Day 43			
08:00	-17.53	-21.80	4.28 (1.66, 6.89)
10:00	-18.62	-20.20	1.58 (-1.08, 4.24)
16:00	-17.98	-16.97	-1.01 (-3.89, 1.88)
Day 90			
08:00	-15.58	-20.97	5.39 (2.85, 7.92)
10:00	-14.98	-17.77	2.79 (-0.11, 5.69)
16:00	-15.12	-16.66	1.55 (-1.37, 4.46)

Study ROCKET 2

Study ROCKET 2 was a Phase III, randomised, double-blind, multicentre, 12-month study comparing two dosing regimens of netarsudil with timolol maleate in patients with OAG or OHT in both eyes, and with unmedicated 08:00 hour IOP > 20 mmHg and < 27 mmHg in the study eye.

Patients were randomised in a 1:1:1 ratio to receive netarsudil 0.02% once daily in the evening, netarsudil 0.02% twice daily or timolol maleate 0.5% twice daily for 12 months. The primary efficacy endpoint was the mean IOP of subjects with baseline IOP < 25 mmHg, at 08:00, 10:00, and 16:00 hours on Day 15, Day 43 and Day 90. The study design, statistical methods and non-inferiority margin were similar to that of Study ROCKET 1.

A total of 756 patients were randomised in the study: 251 subjects each in the netarsudil once daily and timolol arms and 254 subjects in the netarsudil twice daily arm. The demographic and baseline characteristics of subjects were generally well-balanced across treatment groups. The mean age was 64.1 years (range 11 to 92 years), the majority of subjects were female (61.2%) and White (68.9%), and 1.9% of subjects were Asian. Study eye diagnosis was OAG for 65.6% and OHT for 34.4% of enrolled patients. Use of PGAs was reported for 49.1% of subjects. No other ocular medication was used by more than 10% of subjects. Mean IOP at screening was 19.9, 20.0 and 20.1 mmHg in the netarsudil once daily, netarsudil twice daily and timolol arms, respectively.

Non-inferiority of netarsudil once daily and twice daily arms to timolol arm was demonstrated in both the PP and ITT populations with maximum baseline IOP < 25 mmHg (Table 5). In the PP population with maximum baseline IOP < 25 mmHg, the upper 95% CI for the differences in mean IOP between netarsudil once daily and timolol was within 1.5 mmHg at all the 9 timepoints and within 1.0 mmHg at 6 of the 9 timepoints, and between netarsudil twice daily and timolol was within 1.0 mmHg at all the 9 timepoints, therefore meeting the pre-specified criteria for noninferiority. Similarly, in the ITT population with baseline IOP < 25 mmHg, the upper 95% CI for the differences in mean IOP between netarsudil once daily and timolol arms was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 7 of the 9 time points, and between netarsudil twice daily and timolol arms was within 1.0 mmHg at all of the 9 time points.

In patients with baseline IOP ≥ 25 mmHg and < 27 mmHg, both dosing regimens of netarsudil demonstrated reductions in IOP at all timepoints, but non-inferiority to timolol was not demonstrated (Table 6).

At each post-baseline visit, the mean percent reduction from baseline IOP in the PP population with maximum baseline IOP < 25 mmHg ranged from 16.03% to 21.33% in the netarsudil once

daily group, 19.56% to 23.81% in the netarsudil twice daily group, and 17.76% to 22.52% in the timolol group (Table 7). The mean diurnal IOPs at Days 15, 43, and 90 were 17.16, 17.29, and 17.44 mmHg and 16.39, 16.48, and 16.99 mmHg in the netarsudil once daily and twice daily groups, respectively, and 17.15, 16.90, and 17.12 mmHg in the timolol group. The mean changes from baseline for mean diurnal IOP at Days 15, 43, and 90 were -4.30, -4.16, and -3.97 mmHg in the netarsudil once daily group, -5.10, -5.01, and -4.52 mmHg in the netarsudil twice daily group, and -4.36, -4.62, and -4.40 mmHg in the timolol group, respectively, which were all statistically significant (p<0.0001). The difference in mean diurnal IOP between netarsudil twice daily vs timolol was statistically significant at Day 15 in favour of netarsudil twice daily (p=0.013), but not at Day 43 (p=0.163) or Day 90 (p=0.720). The difference in mean diurnal IOP between netarsudil once daily vs timolol was not statistically significant at Day 15 (p=0.979), Day 43 (p=0.168) or Day 90 (p=0.319).

Table 5 [ROCKET 2]: Study eye IOP (mmHg) by Visit (PP Population with observed data-baseline IOP < 25)

Day and Time	Mean IOP Netarsudil OD N=129	Mean IOP Netarsudil BD N=132	Mean IOP Timolol N=142	Mean difference (95% CI) Netarsudil OD - Timolol	Mean difference (95% CI) Netarsudil BD - Timolol
Baseline					
08:00	22.54	22.55	22.54		
10:00	21.29	21.27	21.27		
16:00	20.43	20.56	20.71		
Day 15					
08:00	18.07	17.21	17.69	0.37 (-0.25, 0.99)	-0.48 (-1.19, 0.22)
10:00	16.72	16.35	16.93	-0.21 (-0.82, 0.41)	-0.57 (-1.24, 0.09)
16:00	16.68	15.65	16.83	-0.15 (-0.75, 0.46)	-1.18 (-1.82, -0.54)
Day 43					
08:00	17.95	17.64	17.46	0.49 (-0.13, 1.12)	0.17 (-0.51, 0.86)
10:00	16.95	16.28	16.63	0.32 (-0.31, 0.95)	-0.34 (-1.02, 0.33)
16:00	17.00	15.75	16.60	0.40 (-0.22, 1.02)	-0.85 (-1.53, -0.17)
Day 90					
08:00	18.24	17.58	17.47	0.77 (0.03, 1.50)	0.11 (-0.64, 0.86)
10:00	17.03	16.94	16.92	0.10 (-0.59, 0.80)	0.02 (-0.72, 0.77)
16:00	17.13	16.51	16.95	0.18 (-0.55, 0.91)	-0.44 (-1.16, 0.27)

Table 6 [ROCKET 2]: Study eye IOP (mmHg) by Visit (PP Population with observed data-baseline IOP ≥ 25 and < 27) (post-hoc analysis)

Day and Time	Mean IOP Netarsudil OD N=77	Mean IOP Netarsudil BD N=77	Mean IOP Timolol N=75	Mean difference (95% CI) Netarsudil OD - Timolol	Mean difference (95% CI) Netarsudil BD - Timolol
Baseline					
08:00	25.14	25.13	25.18		
10:00	24.02	23.97	23.89		
16:00	23.46	23.07	23.33		
Day 15					
08:00	20.66	19.95	19.31	1.35 (0.44, 2.26)	0.64 (-0.39, 1.67)
10:00	19.49	17.93	18.56	0.93 (-0.08, 1.93)	-0.63 (-1.67, 0.41)
16:00	18.55	17.44	19.05	-0.50 (-1.48, 0.48)	-1.61 (-2.64, -0.58)
Day 43					
08:00	21.80	20.34	19.26	2.55 (1.41, 3.68)	1.09 (0.12, 2.06)
10:00	20.19	18.62	18.61	1.58 (0.51, 2.65)	0.01 (-1.02, 1.03)
16:00	19.46	18.15	18.49	0.97 (0.01, 1.93)	-0.34 (-1.40, 0.71)

Day 90					
08:00	21.69	20.77	19.62	2.07 (0.95, 3.18)	1.14 (-0.03, 2.32)
10:00	20.41	19.57	18.67	1.74 (0.60, 2.87)	0.90 (-0.35, 2.15)
16:00	18.96	18.26	19.03	-0.08 (-1.23, 1.07)	-0.78 (-2.06, 0.50)

Table 7 [ROCKET 2]: Mean Percent Change from Diurnally Adjusted Baseline in Study Eye IOP by Visit (PP Population with observed data-baseline IOP < 25)

Day and Time	Mean percent change in IOP Netarsudil OD N=129	Mean percent change in IOP Netarsudil BID N=132	Mean percent change in IOP Timolol N=142	Mean difference (95% CI) Netarsudil OD - Timolol	Mean difference (95% CI) Netarsudil BID - Timolol
Day 15					
08:00	-19.94	-23.81	-21.48	1.54 (-1.12, 4.20)	-2.33 (-5.29, 0.63)
10:00	-21.33	-23.18	-20.34	-0.99 (-3.81, 1.84)	-2.84 (-5.91, 0.23)
16:00	-18.27	-23.55	-18.37	0.09 (-2.88, 3.07)	-5.18 (-8.40, -1.95)
Day 43					
08:00	-20.42	-21.84	-22.52	2.10 (-0.51, 4.72)	0.69 (-2.24, 3.61)
10:00	-20.45	-23.54	-21.78	1.33 (-1.51, 4.18)	-1.75 (-4.80, 1.29)
16:00	-16.76	-23.19	-19.52	2.76 (-0.17, 5.69)	-3.67 (-6.95, -0.39)
Day 90					
08:00	-19.18	-22.09	-22.50	3.32 (0.23, 6.41)	0.41 (-2.75, 3.57)
10:00	-19.79	-20.73	-20.38	0.59 (-2.65, 3.83)	-0.35 (-3.72, 3.03)
16:00	-16.03	-19.56	-17.76	1.73 (-1.69, 5.15)	-1.80 (-5.28, 1.68)

Study ROCKET 4

Study ROCKET 4 was a Phase III, randomised, double-blind, multicentre, 6-month study comparing netarsudil with timolol maleate in patients with OAG or OHT in both eyes, and with unmedicated 08:00 hour IOP > 20 mmHg and < 30 mmHg in the study eye.

Patients were randomised in a 1:1 ratio to receive netarsudil 0.02% once daily in the evening or timolol maleate 0.5% twice daily for 6 months. The primary efficacy endpoint was the mean IOP of subjects with baseline IOP < 25 mmHg, at 08:00, 10:00, and 16:00 hours on Day 15, Day 43 and Day 90. The study design, statistical methods and non-inferiority margin were similar to that of Study ROCKET 1.

A total of 708 patients were randomised in the study: 351 subjects in the netarsudil arm and 357 in the timolol arm. The mean age was 64.3 years (range 18 to 91 years), the majority of subjects were female (62.9%) and White (75.3%), and 1.8% of subjects were Asian. Study eye diagnosis was OAG for 66.0% and OHT for 34.0% of enrolled patients. Use of PGAs was reported for 52.5% of subjects. No other ocular medication was used by more than 10% of subjects. Mean IOP at screening was 20.0 and 20.2 mmHg in the netarsudil and timolol treatment arms, respectively.

Non-inferiority of netarsudil to timolol was demonstrated in both the PP and ITT populations with maximum baseline IOP < 25 mmHg (Table 8). In the PP population with maximum baseline IOP < 25 mmHg, the upper 95% CI for the differences in mean IOP between netarsudil and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 8 of the 9 time points, hence meeting the pre-specified criteria for non-inferiority. Similarly, in the ITT population with baseline IOP < 25 mmHg, the upper 95% CI for the differences in mean IOP between netarsudil and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 8 of the 9 time points.

In patients with baseline IOP ≥ 25 mmHg and < 30 mmHg, netarsudil demonstrated reductions in IOP at all timepoints, but non-inferiority to timolol was not demonstrated (Table 9).

At each post-baseline visit, the mean percent reduction from baseline IOP in the PP population with maximum baseline IOP < 25 mmHg ranged from 18.69% to 21.38% in the netarsudil group and 18.05% to 22.88% in the timolol group (Table 10). The mean diurnal IOPs at Days 15, 43, and 90 were 16.83, 17.03, and 17.15 mmHg in the netarsudil group and 17.04, 17.08, and 16.93 mmHg in the timolol group, respectively. The mean changes from baseline for mean diurnal IOP at Days 15, 43, and 90 were -4.56, -4.32, and -4.19 mmHg in the netarsudil group, and -4.42, -4.39, and -4.54 mmHg in the timolol group, respectively, which were all statistically significant (p<0.0001). The difference in mean diurnal IOP between treatment groups was not statistically significant at Day 15 (p=0.402), Day 43 (p=0.863) or Day 90 (p=0.413).

Table 8 [ROCKET 4]: Study eye IOP (mmHg) by Visit (PP Population with observed data-baseline IOP < 25)

Day and Time	Mean IOP Netarsudil N=186	Mean IOP Timolol N=186	Mean difference (95% CI) Netarsudil - Timolol
Baseline			
08:00	22.40	22.44	
10:00	21.06	21.27	
16:00	20.69	20.69	
Day 15			
08:00	17.68	17.51	0.17 (-0.43, 0.77)
10:00	16.55	16.71	-0.16 (-0.73, 0.41)
16:00	16.32	16.92	-0.60 (-1.16, -0.04)
Day 43			
08:00	17.84	17.60	0.25 (-0.34, 0.83)
10:00	16.75	16.98	-0.22 (-0.82, 0.37)
16:00	16.57	16.67	-0.10 (-0.66, 0.46)
Day 90			
08:00	17.86	17.29	0.56 (-0.02, 1.15)
10:00	16.90	16.69	0.21 (-0.37, 0.79)
16:00	16.73	16.80	-0.07 (-0.68, 0.55)

Table 9 [ROCKET 4]: Study eye IOP (mmHg) by Visit (PP Population with observed data-baseline IOP ≥ 25 and < 30) (post-hoc analysis)

Day and Time	Mean IOP Netarsudil N=120	Mean IOP Timolol N=130	Mean difference (95% CI) Netarsudil - Timolol
Baseline			
08:00	26.30	25.96	
10:00	25.18	24.91	
16:00	24.48	23.99	
Day 15			
08:00	21.57	20.15	1.42 (0.51, 2.34)
10:00	20.09	19.34	0.75 (-0.15, 1.64)
16:00	20.01	19.17	0.83 (0.00, 1.67)
Day 43			
08:00	21.99	19.84	2.14 (1.16, 3.13)
10:00	20.33	19.19	1.15 (0.30, 1.99)
16:00	20.03	19.63	0.41 (-0.47, 1.29)
Day 90			
08:00	21.71	19.91	1.79 (0.74, 2.85)
10:00	20.80	18.95	1.85 (0.89, 2.81)
16:00	20.31	18.94	1.37 (0.46, 2.28)

Table 10 [ROCKET 4]: Mean Percent Change from Diurnally Adjusted Baseline in Study Eye IOP by Visit (PP Population with observed data-baseline IOP < 25)

Day and Time	Mean percent change in IOP Netarsudil N=186	Mean percent change in IOP Timolol N=186	Mean difference (95% CI) Netarsudil - Timolol
Day 15			
08:00	-21.20	-21.92	0.72 (-1.86, 3.29)
10:00	-21.38	-21.30	-0.07 (-2.54, 2.40)
16:00	-21.01	-18.05	-2.96 (-5.37, -0.55)
Day 43			
08:00	-20.41	-21.51	1.10 (-1.36, 3.55)
10:00	-20.30	-20.04	-0.26 (-2.81, 2.29)
16:00	-19.66	-19.25	-0.41 (-2.88, 2.05)
Day 90			
08:00	-20.26	-22.88	2.62 (0.11, 5.14)
10:00	-19.41	-21.37	1.96 (-0.60, 4.52)
16:00	-18.69	-18.61	-0.08 (-2.81, 2.64)

Across the pivotal Phase III studies, non-inferiority of netarsudil 0.02% to timolol 0.5% was demonstrated only in the subgroup population with baseline IOP <25 mmHg. Based on a pooled analysis of the Phase III studies, the magnitude of IOP reduction with netarsudil was broadly similar in the following baseline IOP subgroups: -4.05 to -4.57 mmHg in subjects with baseline IOP < 25 mmHg and -3.71 to -4.71 mmHg in subjects with baseline IOP ≥ 25 and < 30 mmHg. This suggests that netarsudil was similarly effective at lowering IOP in subjects with higher baseline IOP compared to those with lower baseline IOP.

Patients with baseline IOP ≥ 30 mmHg were not studied in the pivotal Phase III studies. Nevertheless, the efficacy of netarsudil at baseline IOP ≥ 30 mmHg was supported by Phase III studies performed for the fixed-dose combination of netarsudil and latanoprost, whereby subjects who received netarsudil demonstrated IOP reductions of -5.74 to -6.35 mmHg in the subgroup with baseline IOP ≥ 30 and < 36mmHg.

Overall, the submitted efficacy data adequately supported the use of netarsudil for the reduction of elevated IOP in patients with primary open-angle glaucoma or ocular hypertension. As patients with pseudo-exfoliative or pigmentary glaucoma were excluded from the Phase III studies, the use of netarsudil in patients with secondary glaucoma such as pseudo-exfoliative or pigmentary glaucoma has not been studied, hence primary open-angle glaucoma is specified in the indication.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of netarsudil was based primarily on safety data derived from the three pivotal Phase III studies, ROCKET 1, ROCKET 2 and ROCKET 3, comprising a total of 1,874 patients who received at least one dose of study treatment: 805 subjects in the netarsudil once daily arm, 253 subjects in the netarsudil twice daily arm and 816 subjects in the timolol arm. The mean duration of treatment in the netarsudil 0.02% once daily vs timolol 0.05% arm was 83 vs 87 days (ROCKET 1), 260 vs 325 days (ROCKET 2), and 147 vs 168 days (ROCKET 3), respectively.

Overview of safety profile (ROCKET 1)

Adverse Event (AE)	Netarsudil QD (N=203) n (%)	Timolol (N=208) n (%)
Any AE	165 (81.3)	112 (53.8)
Treatment-related AE	148 (72.9)	89 (42.8)
Ocular AE	156 (76.8)	92 (44.2)
Non-ocular AE	41 (20.2)	40 (19.2)
SAE	3 (1.5)	4 (1.9)
Treatment-related SAE	1 (0.5)	0
Discontinuations due to AE	22 (10.8)	4 (1.9)
Deaths	0	0

Overview of safety profile (ROCKET 2)

AE	Netarsudil QD (N=251) n (%)	Netarsudil BD (N=253) n (%)	Timolol (N=251) n (%)
Any AE	220 (87.6)	225 (88.9)	159 (63.3)
Treatment-related AE	192 (76.5)	207 (81.8)	98 (39.0)
Ocular AE	209 (83.3)	222 (87.7)	124 (49.4)
Non-ocular AE	81 (32.3)	68 (26.9)	82 (32.7)
SAE	17 (6.8)	7 (2.8)	12 (4.8)
Treatment-related SAE	0	0	0
Discontinuations due to AE	76 (30.3)	136 (53.8)	16 (6.4)
Deaths	2 (0.8)	0	0

Overview of safety profile (ROCKET 4)

AE	Netarsudil OD (N=351) n (%)	Timolol (N=357) n (%)
Any AE	281 (80.1)	215 (60.2)
Treatment-related AE	241 (68.7)	152 (42.6)
Ocular AE	267 (76.1)	180 (50.4)
Non-ocular AE	82 (23.4)	91 (25.5)
SAE	8 (2.3)	10 (2.8)
Treatment-related SAE	0	0
Discontinuations due to AE	71 (20.2)	11 (3.1)
Deaths	1 (0.3)	0

Across the three pivotal studies, the majority (>80%) of subjects in the netarsudil arm experienced an adverse event (AE). Overall, most AEs associated with the use of netarsudil were local ocular side effects. In a pooled analysis of the three Phase III studies, ocular AEs were reported in 78.5% of subjects in the netarsudil once daily arm vs 48.5% in the timolol arm. The most frequently reported ocular AEs in the netarsudil once daily group (and their incidences vs timolol) were conjunctival hyperaemia (53.2% vs 10.4%), corneal verticillata (20.1% vs 0.2%), instillation site pain (19.6% vs 21.4%), and conjunctival haemorrhage (17.0% vs 1.8%). While the ocular AEs occurring with netarsudil were generally mild or moderate and often resolved spontaneously, the higher frequency of ocular AEs (78.5% vs 48.5%) and higher discontinuation rates (21.0% vs 3.8%) in the netarsudil once daily arm compared to the timolol arm suggests lower overall tolerability of netarsudil.

The ocular safety profile of netarsudil was broadly consistent with the safety profile of Rho kinase inhibitors, except for the occurrence of corneal verticillata, which was not observed with the other Rho kinase inhibitor. In the follow-up observational study AR-13324-OBS01, most

corneal verticillata cases resolved spontaneously without an impact on visual acuity. Information on ocular AEs, including the occurrence of corneal verticillata in the clinical studies, have been included in the package insert.

The role of the preservative, benzalkonium chloride, in contributing to the overall nature and frequency of ocular AEs, such as eye irritation, dry eyes, disruption of the tear film and corneal surface, in the netarsudil groups was difficult to quantify. Benzalkonium chloride has been used in similar concentrations in other ophthalmic products for glaucoma treatment. Warnings on the presence of benzalkonium chloride and its possible AEs have been included in the package insert.

Systemic AEs occurred infrequently in the Phase III studies and at a similar rate between the netarsudil and timolol groups (25.3% vs 26.1%). Serious AEs (SAEs) were reported at low and comparable incidences between the netarsudil and timolol groups (3.5% vs 3.2%). Although one serious AE (exacerbation of coronary artery disease) in the netarsudil group was considered possibly related to treatment, the event was confounded by multiple comorbid medical conditions and causality cannot be reliably established. There were no deaths considered by investigators to be related to study treatment.

Overall, the safety profile of netarsudil was assessed to be manageable, and no major concerns were raised. As the pivotal studies were conducted for up to 12 months but anti-glaucoma topical agents are indicated for chronic use, long-term safety data from the post-authorisation safety study would be required to assess the longer-term safety profile of netarsudil. The planned study is a non-interventional, observational, ocular safety study of 2 years of treatment with netarsudil in patients with elevated IOP due to POAG or OHT.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The goal of POAG and OHT treatment is to lower intraocular IOP to preserve visual function. Prostaglandin analogues are the most frequently prescribed eye drops for lowering IOP in glaucoma because they are most efficacious and well tolerated with a convenient once daily posology. Other topical IOP-lowering therapeutic classes include beta blockers, alfa-2 agonists, carbonic anhydrase inhibitors, cholinergic agonists, and Rho kinase inhibitors. If a drug fails to reduce IOP sufficiently, clinical practice guidelines for the management of glaucoma recommend switching to an alternative medication as monotherapy or adding medication of a different drug class until the desired IOP is attained. Netarsudil belongs to the class of Rho kinase inhibitors.

A high prevalence of glaucoma patients with baseline IOP < 25 mmHg (> 70% in US, Sweden and UK) and normotension glaucoma defined as IOP ≤ 21 mmHg (> 50% in Asian countries) have been reported. Locally, experts estimated the overall prevalence of OHT and/or POAG patients with baseline IOP < 25 mmHg to be in the range of 20% to 70%.

In the pivotal studies ROCKET 1, ROCKET 2 and ROCKET 4, the non-inferiority of netarsudil 0.02% to timolol 0.5%, based on mean IOP at Day 15 through Day 90, has been demonstrated in patient populations with a baseline IOP < 25 mmHg, but not in the total study population with maximum baseline IOP < 30 mmHg. The failure to demonstrate non-inferiority of netarsudil to timolol suggests potential limited clinical utility of netarsudil relative to timolol in subjects with baseline IOP > 25 mmHg. Nonetheless, the mean IOP reduction with netarsudil in the pooled Phase III studies was -3.71 to -4.71 mmHg in subjects with baseline IOP ≥ 25 and < 30 mmHg,

which was regarded to be clinically relevant. The once daily dosing frequency with netarsudil may potentially improve patient adherence.

The ocular safety profile of netarsudil was mostly consistent with that of the class of Rho kinase inhibitors. The ocular AEs reported with netarsudil were generally mild or moderate in severity and mostly resolved spontaneously. Corneal verticillata, which occurred in 19% of subjects from the three pivotal studies, was further characterised in a follow-up observational study in which most cases resolved spontaneously without an impact on visual acuity. These risks have been adequately presented in the package insert. Systemic AEs were reported at low and comparable incidences between the netarsudil and timolol groups.

The overall benefit-risk profile of netarsudil was considered favourable for the reduction of elevated IOP in adult patients with primary open-angle glaucoma or ocular hypertension. Longer-term data from the post-authorisation safety study would be required to further characterise the safety profile.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Rhopressa Ophthalmic Solution 0.02% w/v for the reduction of elevated IOP in patients with primary open-angle glaucoma or ocular hypertension was deemed favourable and approval of the product registration was granted on 4 July 2023. The approval of this application is subject to the submission of the final study report of the post-authorisation safety study to confirm the longer-term safety profile of netarsudil.

APPROVED PACKAGE INSERT AT REGISTRATION

RHOPRESSA OPHTHALMIC SOLUTION, 0.02% W/V
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 primary open-angle glaucoma or ocular hypertension *[see section 12 Clinical Studies].*

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.

Due to netarsudil's vasodilating properties, other eye drops should be administered before netarsudil. Eye ointments should be administered last.

3. DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 0.2 mg/mL of netarsudil.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

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.

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.

5.3 Benzalkonium chloride content

This medicinal product contains benzalkonium chloride.
Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface and is known to discolour soft contact lenses. It should be used with caution in dry eye patients and in patients where the cornea may be compromised.
Patients should be monitored in case of prolonged use.

5.4 Long term use

The efficacy and safety of netarsudil has not been studied beyond 12 months.

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. The incidence of cornea verticillata was higher in certain subpopulations: elderly (≥65 years) versus non-elderly (24.8 vs. 15.9%); males versus females (24.4 vs. 18.4%) and in white versus other races (25.6 vs. 7.0%).

Tabulated list of adverse reactions

The following adverse reactions have been reported with netarsudil, dosed once daily. Reactions are classified according to the convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data).

System Organ Classification	**Frequency**	**Adverse reactions**
Immune system disorders	Uncommon	hypersensitivity
Nervous system disorders	Common	headache
	Uncommon	dizziness, visual field defect
Eye disorders	Very common	conjunctival hyperaemia[1], cornea verticillata[1], instillation site pain
	Common	conjunctival haemorrhage, vision blurred, lacrimation increased, erythema of eyelid, eye pruritis, eye irritation, visual acuity reduced, eyelid oedema, punctate keratitis, conjunctival oedema, foreign body sensation in eyes, conjunctivitis, conjunctivitis allergic, photophobia, eyelid pruritus, eye pain, corneal opacity, dry eye, eye discharge, instillation site erythema, instillation site discomfort, instillation site pruritis, vital dye staining cornea present, intraocular pressure increased
	Uncommon	ocular hyperaemia, blepharitis, corneal disorder, eyelid margin crusting, eye allergy, conjunctival follicles, ocular discomfort, eye swelling, corneal deposits, eyelid disorder, meibomian gland dysfuntion, corneal pigmentation, diplopia, ectropion, lenticular opacities, noninfective conjunctivitis, abnormal sensation in the eye, asthenopia, episcleral hyperaemia, halo vision, keratitis, refraction disorder, anterior chamber flare, anterior chamber inflammation, blindness, conjunctival irritation, conjunctivochalasis, diabetic retinopathy, eczema eyelids, eyelid skin dryness, glaucoma, growth of eyelashes, iris adhesions, iris bombe, iritis, ocular hypertension, visual impairment, corneal dystrophy, instillation site foreign body sensation, instillation site irritation, glassy eyes, fatigue, instillation site dryness, instillation site oedema, instillation site paraesthesia, conjunctival staining, optic nerve cup/disc ratio increased, madarosis
Respiratory, thoracic and mediastinal disorders	Uncommon	nasal discomfort, rhinalgia
Skin and subcutaneous tissue disorders	Uncommon	dermatitis allergic, dermatitis contact, lichenification, petechiae
Musculoskeletal and connective tissue disorders	Uncommon	polychondritis
Injury, poisoning and procedural complications	Uncommon	excoriation

[1] See *ADVERSE REACTIONS, Clinical Trials Experience* for further information

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]*. 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}).

Rhopressa should not be used during pregnancy unless the clinical condition of the woman requires treatment with netarsudil.

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]*, 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.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rhopressa therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

With the exception of corneal verticillata *[see section 6.1]*, no overall differences in the safety or effectiveness profile for Rhopressa has been observed between subjects aged <65 or ≥65 years.

8.6 Compromised corneal epithelium or co-existing ocular pathologies

The efficacy and safety of netarsudil in subjects with compromised corneal epithelium or co-existing ocular pathologies e.g. pseudoexfoliation and pigment dispersion syndrome has not been established.

8.7 Effects on ability to drive and use machines

Rhopressa has negligible influence on the ability to drive and use machines.

If transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines

8.8 Interaction with other medicinal products and other forms of interaction

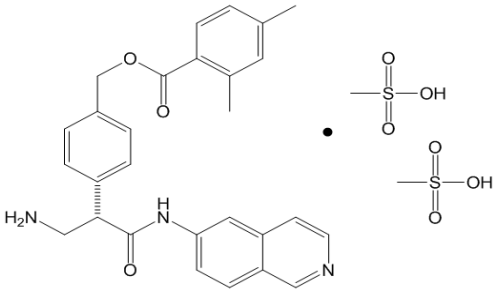
No interaction studies have been performed.

8.9 Overdose

Systemic exposure to netarsudil following topical ocular administration has been shown to be negligible. If topical overdose of netarsudil should occur, the eye(s) may be flushed with tap water. Treatment of an overdose would include supportive and symptomatic therapy.

9. 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 mesylate 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 mesylate is 645.74. The chemical structure is:



Netarsudil mesylate 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 clear, sterile aqueous ophthalmic solution of netarsudil mesylate with pH 4.2-5.2 and osmolality 250-340 mOsm/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 mesylate). 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.

10. CLINICAL PHARMACOLOGY

ATC code: S01EX05

10.1 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.

10.2 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 to AR-13503.

11. NONCLINICAL TOXICOLOGY

11.1 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.

Netarsudil and its active metabolite AR-13503 was found to have a possible phototoxic potential in a modified 3T3 NRU-PT *in vitro* assay, where the wavelength was extended to include UVB light.

12. 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.

Study CS301

A randomised, double-blind, multicentre Phase 3 clinical trial compared the efficacy and safety of netarsudil once daily with that of timolol maleate 0.5% twice daily in reducing IOP in a total of 411 patients with open-angle glaucoma or ocular hypertension. The median age of study participants was 65.0 years (range 20 to 96 years).

The study was designed to show non-inferiority of netarsudil when dosed once daily in the evening to timolol maleate 0.5% dosed twice daily in patients with a baseline IOP of >20 mmHg and <27 mmHg. The primary efficacy outcome measure was mean IOP at each of 9 timepoints measured at 08:00, 10:00 and 16:00 on day 15, day 43 and day 90. The non-inferiority margin applied was a difference in mean IOP ≤1.5 mmHg for all time points over all visits through 3 months and ≤1.0 mmHg at a majority of these time points. Noninferiority of netarsudil to timolol maleate 0.5% was not demonstrated in the overall PP population (baseline IOP < 27 mmHg). The IOP reduction with netarsudil dosed once daily was non-inferior to the effect of timolol 0.5% dosed twice daily in patients with baseline IOP of <25 mmHg (Table 1). Efficacy was also investigated in patients with baseline IOP ≥25 mmHg and <27 mmHg. Netarsudil demonstrated clinically relevant reductions in IOP at all timepoints, however non-inferiority to timolol was not demonstrated in this population with baseline IOP ≥25 mmHg and <30 mmHg (Table 2).

Table 1: Mean IOP by visit: PP population with baseline IOP <25 mmHg (Study CS301)

Study Visit and Time Point		Netarsudil 0.02% Once daily		Timolol 0.5% twice daily		Difference (95% CI) Netarsudil – Timolol
		N	IOP	N	IOP	
Baseline	08:00	113	22.39	124	22.50	
	10:00	113	21.28	124	21.07	
	16:00	113	20.62	124	20.52	
Day 15	08:00	108	17.34	123	17.78	-0.44 (-1.10, 0.22)
	10:00	107	16.18	122	16.98	-0.81 (-1.44, -0.17)
	16:00	107	16.22	122	17.14	-0.92 (-1.58, -0.26)
Day 43	08:00	105	17.85	121	17.81	0.05 (-0.68, 0.77)
	10:00	105	16.88	121	16.96	-0.08 (-0.74, 0.58)
	16:00	105	16.57	120	17.26	-0.69 (-1.40, 0.02)
Day 90	08:00	99	18.22	119	17.91	0.31 (-0.40, 1.02)
	10:00	99	17.34	119	17.43	-0.09 (-0.82, 0.63)

	16:00	99	17.02	119	17.37	-0.35 (-1.03, 0.34)

Table 2: Mean IOP by visit: PP population with baseline IOP ≥25 and <27 mmHg (Study CS301)

Study Visit and Time Point		Netarsudil 0.02% Once daily		Timolol 0.5% twice daily		Difference (95% CI) Netarsudil – Timolol
		N	IOP	N	IOP	
Baseline	08:00	69	25.11	64	25.05	
	10:00	69	23.92	64	23.58	
	16:00	69	23.68	64	23.25	
Day 15	08:00	69	20.78	64	19.41	1.38 (0.36, 2.39)
	10:00	69	19.01	64	18.62	0.40 (-0.70, 1.49)
	16:00	69	18.82	64	18.75	0.07 (-1.04, 1.18)
Day 43	08:00	65	21.78	63	19.09	2.69 (1.53, 3.84)
	10:00	65	20.17	63	18.37	1.80 (0.60, 3.00)
	16:00	65	19.95	63	18.56	1.39 (0.18, 2.60)
Day 90	08:00	58	22.52	62	19.56	2.96 (1.83, 4.09)
	10:00	59	21.58	62	18.98	2.59 (1.48, 3.71)
	16:00	59	20.93	62	18.46	2.47 (1.32, 3.63)

Study CS302

A randomised, double-blind, multicentre Phase 3 clinical trial compared the efficacy and safety of netarsudil once daily and twice daily with that of timolol maleate 0.5% twice daily in reducing IOP in a total of 756 patients with open-angle glaucoma or ocular hypertension. The median age of study participants was 64.1 years (range 11 to 92 years).

The study was designed to show non-inferiority of netarsudil when dosed once daily in the evening and twice daily to timolol maleate 0.5% dosed twice daily in patients with a baseline IOP of >20 mmHg and <27 mmHg. The primary efficacy outcome measure was mean IOP at each of 9 timepoints measured at 08:00, 10:00 and 16:00 on day 15, day 43 and day 90 in patients with baseline IOP < 25 mmHg. The non-inferiority margin applied was a difference in mean IOP ≤1.5 mmHg for all time points over all visits through 3 months and ≤1.0 mmHg at a majority of these time points. The IOP reduction with netarsudil dosed once daily was non-inferior to the effect of timolol 0.5% dosed twice daily in patients with baseline IOP of <25 mmHg (Table 3). Efficacy was also investigated in patients with baseline IOP ≥25 mmHg and <27 mmHg. Netarsudil demonstrated clinically relevant reductions in IOP at all timepoints, however non-inferiority to timolol was not demonstrated in this population with baseline IOP ≥25 mmHg and <27 mmHg (Table 4).

Table 3: Mean IOP by visit: PP population with baseline IOP <25 mmHg (Study CS302)

Study Visit and Time Point		Netarsudil 0.02% Once daily		Timolol 0.5% twice daily		Difference (95% CI) Netarsudil – Timolol
		N	IOP	N	IOP	
Baseline	08:00	129	22.54	142	22.54	
	10:00	129	21.29	142	21.27	
	16:00	129	20.43	142	20.71	
Day 15	08:00	127	18.07	142	17.69	0.37 (-0.26, 0.99)
	10:00	126	16.72	141	16.93	-0.21 (-0.82, 0.41)
	16:00	126	16.68	141	16.83	-0.15 (-0.75, 0.46)
Day 43	08:00	122	17.95	141	17.46	0.49 (-0.13, 1.12)
	10:00	120	16.95	141	16.63	0.32 (-0.31, 0.95)
	16:00	120	17.00	141	16.60	0.40 (-0.22, 1.02)
Day 90	08:00	116	18.24	140	17.47	0.77 (0.03, 1.50)
	10:00	114	17.03	140	16.92	0.10 (-0.59, 0.80)
	16:00	114	17.13	139	16.95	0.18 (-0.55, 0.91)

Table 4: Mean IOP by visit: PP population with baseline IOP ≥25 and <27 mmHg (Study CS302)

Study Visit and Time Point	Netarsudil 0.02% Once daily	Timolol 0.5% twice daily	Difference (95% CI) Netarsudil – Timolol

		N	IOP	N	IOP	
Baseline	08:00	77	25.14	75	25.18	
	10:00	77	24.02	75	23.89	
	16:00	77	23.46	75	23.33	
Day 15	08:00	74	20.66	75	19.31	1.35 (0.44, 2.26)
	10:00	73	19.49	74	18.56	0.93 (-0.08, 1.93)
	16:00	74	18.55	74	19.05	-0.50 (-1.48, 0.48)
Day 43	08:00	71	21.80	74	19.26	2.55 (1.41, 3.68)
	10:00	67	20.19	74	18.61	1.58 (0.51, 2.65)
	16:00	67	19.46	74	18.49	0.97 (0.01, 1.93)
Day 90	08:00	61	21.69	74	19.62	2.07 (0.95, 3.18)
	10:00	59	20.41	73	18.67	1.74 (0.60, 2.87)
	16:00	56	18.96	73	19.03	-0.08 (-1.23, 1.07)

Study CS304

A randomised, double-blind, multicentre Phase 3 clinical trial compared the efficacy and safety of netarsudil once daily with that of timolol maleate 0.5% twice daily in reducing IOP in a total of 708 patients with open-angle glaucoma or ocular hypertension. The median age of study participants was 65.5 years (range 18 to 91 years).

The study was designed to show non-inferiority of netarsudil when dosed once daily in the evening to timolol maleate 0.5% dosed twice daily in patients with a baseline IOP of >20 mmHg and <25 mmHg. The primary efficacy outcome measure was mean IOP at each of 9 timepoints measured at 08:00, 10:00 and 16:00 on day 15, day 43 and day 90 in patients with baseline IOP < 25 mmHg. The non-inferiority margin applied was a difference in mean IOP ≤1.5 mmHg for all time points over all visits through 3 months and ≤1.0 mmHg at a majority of these time points. The IOP reduction with netarsudil dosed once daily was non-inferior to the effect of timolol 0.5% dosed twice daily in patients with baseline IOP of <25 mmHg (Table 5). Efficacy was also investigated in patients with baseline IOP ≥25 mmHg and <30 mmHg. Netarsudil demonstrated clinically relevant reductions in IOP at all timepoints, however non-inferiority to timolol was not demonstrated in this population with baseline IOP ≥25 mmHg and <30 mmHg (Table 6).

Table 5: Mean IOP by visit: PP population with baseline IOP <25 mmHg (Study CS304)

Study Visit and Time Point		Netarsudil 0.02% Once daily		Timolol 0.5% twice daily		Difference (95% CI) Netarsudil – Timolol
		N	IOP	N	IOP	
Baseline	08:00	186	22.40	186	22.44	
	10:00	186	21.06	186	21.27	
	16:00	186	20.69	186	20.69	
Day 15	08:00	184	17.68	183	17.51	0.17 (-0.43, 0.77)
	10:00	181	16.55	183	16.71	-0.16 (-0.73, 0.41)
	16:00	181	16.32	183	16.92	-0.60 (-1.16, -0.04)
Day 43	08:00	177	17.84	183	17.60	0.25 (-0.34, 0.83)
	10:00	177	16.75	182	16.98	-0.22 (-0.82, 0.37)
	16:00	176	16.57	182	16.67	-0.10 (-0.66, 0.46)
Day 90	08:00	167	17.86	179	17.29	0.56 (-0.02, 1.15)
	10:00	166	16.90	179	16.69	0.21 (-0.37, 0.79)
	16:00	165	16.73	179	16.80	-0.07 (-0.68, 0.55)

Table 6: Mean IOP by visit: PP population with baseline IOP ≥25 and <30 mmHg (Study CS304)

Study Visit and Time Point		Netarsudil 0.02% Once daily		Timolol 0.5% twice daily		Difference (95% CI) Netarsudil – Timolol
		N	IOP	N	IOP	
Baseline	08:00	120	26.30	130	25.96	
	10:00	120	25.18	130	24.91	
	16:00	120	24.48	130	23.99	
Day 15	08:00	118	21.57	129	20.15	1.42 (0.51, 2.34)
	10:00	116	20.09	129	19.34	0.75 (-0.15, 1.64)

	16:00	116	20.01	129	19.17	0.83 (0.00, 1.67)
Day 43	08:00	112	21.99	127	19.84	2.14 (1.16, 3.13)
	10:00	109	20.33	127	19.19	1.15 (0.30, 1.99)
	16:00	109	20.03	127	19.63	0.41 (-0.47, 1.29)
Day 90	08:00	94	21.71	121	19.91	1.79 (0.74, 2.85)
	10:00	93	20.80	120	18.95	1.85 (0.89, 2.81)
	16:00	93	20.31	120	18.94	1.37 (0.46, 2.28)

The safety of netarsudil has been evaluated in clinical studies, including four well-controlled Phase 3 studies.

Approximately 75% of subjects included in the netarsudil treatment groups of Phase 3 studies were Caucasian and 24% Black or African American. Over half were aged ≥ 65 years. With the exception of the incidence of cornea verticillata, no other difference in safety profile was observed between races or age groups (see section 6.1).

Completion rates in Phase 3 studies were lower in the netarsudil treatment group when compared with the timolol maleate group. Subjects with known contraindications or hypersensitivity to timolol were excluded from the studies. Discontinuation rates due to adverse reactions were 19.3% for the netarsudil treatment group versus 1.7% for the timolol maleate group. The majority of discontinuations in the netarsudil group were associated with ocular adverse reactions, whereas the majority of discontinuations in the timolol group were associated with non-ocular adverse reactions. The most frequently reported adverse reactions associated with discontinuation in the netarsudil groups were conjunctival hyperemia (5.8%), cornea verticillata (3.7%) and vision blurred (1.4%). The incidences of hyperemia and vision blurred were sporadic in nature.

The efficacy and safety of netarsudil in subjects with compromised corneal epithelium or co-existing ocular pathologies e.g. pseudoexfoliation and dispersion pigment syndrome has not been established.

13. 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

Storage: Store at 2°C to 8°C until opened. After opening, do not store above 30°C and use within one month.

14. 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].*

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.

15. Manufactured by

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