SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rhokiinsa 200 micrograms/ml eye drops, solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 200 micrograms netarsudil (as mesylate).

Excipient(s) with known effect

Each ml of solution contains 150 micrograms benzalkonium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

Clear solution, pH 5 (approximately).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rhokiinsa is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension.

4.2 Posology and method of administration

Treatment with Rhokiinsa should only be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology.

Posology

The recommended dose is one drop in the affected eye(s) once daily in the evening. Patients should not instill more than one drop in the affected eye(s) each day.

If one dose is missed, treatment should continue with the next dose in the evening.

Paediatric population

The safety and efficacy of Rhokiinsa in children below the age of 18 years have not been established.

No data are available.

Method of administration

For ocular use.

No data on potential interactions specific to netarsudil is currently available (see section 4.5). If netarsudil is to be used concomitantly with other topical ophthalmic medicinal products, each medicinal product should be administered at least five (5) minutes apart. Due to netarsudil's vasodilating properties, other eye drops should be administered before. Eye ointments should be administered last.

Contact lenses should be removed prior to instillation of netarsudil and may be reinserted 15 minutes following its administration (see section 4.4).

The tip of the dispensing container should avoid contacting the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ocular effects

Twice a day dosing is not well tolerated and is not recommended. Netarsudil dosed twice daily provided slightly larger IOP reductions, but had a less favorable safety profile as reflected in a higher rate and increased severity of ocular adverse reactions. Twice a day dosing was also associated with a higher discontinuation rate due to adverse reactions (53.8%) during a 12-month study. It is therefore recommended to dose netarsudil once daily.

Reticular epithelial corneal oedema

Reticular epithelial corneal oedema (RECE) has been reported following administration of medicinal products containing netarsudil, particularly in patients with preexisting corneal oedema or prior ocular surgery. RECE typically resolves upon discontinuation of the medicinal product containing netarsudil. Patients should be advised to notify their physician if they experience decreased vision or eye pain while using Rhokiinsa.

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

Excipients with known effect

Benzalkonium chloride
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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of netarsudil in pregnant women. No effects during pregnancy are anticipated, since systemic exposure to netarsudil is negligible (see section 5.2). Animal studies with intravenous administration do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3). Rhokiinsa should not be used during pregnancy unless the clinical condition of the woman requires treatment with netarsudil.

Breast-feeding

It is unknown whether netarsudil/metabolites are excreted in human milk. However, while no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding women to netarsudil is expected to be negligible, no relevant clinical data are available (see section 5.2). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rhokiinsa therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of netarsudil on male or female fertility. However, no effects are anticipated, since systemic exposure to netarsudil is negligible (see section 5.2).

4.7 Effects on ability to drive and use machines

Rhokiinsa 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.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions observed in the clinical trials were conjunctival hyperemia (51% of patients), cornea verticillata (17%), instillation site pain (17%), conjunctival haemorrhage (8%), instillation site erythema (8%), corneal staining (7%), blurred vision (6%), increased lacrimation (6%) and erythema of eyelid (5%). Serious adverse reactions were not reported in clinical trials.

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
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,

System organ classification	Frequency	Adverse reactions
		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 Visual field defect
	Not known	Reticular epithelial corneal oedema[2]
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 *Description of selected adverse reactions* for further information
[2] Additional adverse reaction observed with netarsudil monotherapy

Description of selected adverse reactions

Conjunctival hyperaemia
Conjunctival hyperaemia was the most frequently reported adverse reaction associated with netarsudil treatment in clinical trials and it is attributed to the vasodilation effect of the Rho kinase inhibitor drug class. Conjunctival hyperaemia was typically mild in severity and sporadic. However, there was a relatively small proportion of subjects with moderate or severe hyperaemia who discontinued treatment because of this adverse reaction (6.0% in Phase 3 clinical trials).

Cornea verticillata
Cornea verticillata occurred in approximately 20% of the patients in controlled Phase 3 clinical trials. The cornea verticillata seen in netarsudil-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. The majority of cornea 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%).

Special populations

Elderly subjects
With the exception of cornea verticillata (see above), no difference in the safety profile for Rhokiinsa has been observed between subjects aged <65 or ≥65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme:
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiglaucoma preparations and miotics, ATC code: S01EX05

Mechanism of action

Netarsudil, a Rho kinase inhibitor, is believed to reduce IOP by increasing outflow of aqueous humor. Studies in animal and man suggest that the main mechanism of action is increased trabecular outflow. These studies also suggest that netarsudil lowers IOP by reducing episcleral venous pressure.

Clinical efficacy and safety

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. 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 1). 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 2).

Table 1: Mean IOP by visit: PP population with baseline IOP <25 mmHg

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 2: Mean IOP by visit: PP population with baseline IOP ≥25 and <30 mmHg

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 trials, 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 4.8).

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 Rhokiinsa 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Rhokiinsa in all subsets of the paediatric population for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The systemic exposures of netarsudil and its active metabolite, AR-13503, were evaluated in 18 healthy subjects after topical ocular administration of netarsudil 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.

Biotransformation

After topical ocular dosing, netarsudil is metabolised by esterases in the eye to an active metabolite, AR-13503.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to development.

Effects in non-clinical trials were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Intravenous administration of netarsudil mesylate to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures. In pregnant rats, 0.3 mg/kg/day (1 000 times the recommended ophthalmic dose) and higher showed increased post-implantation loss and reduced foetal viability. In pregnant rabbits, 3 mg/kg/day (10 000 times the recommended ophthalmic dose) and higher showed an increase in post-implantation loss and a decrease in foetal weight.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil.

Netarsudil was not mutagenic in a bacterial mutation assay, in a mouse lymphoma assay, or in a rat micronucleus test.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Mannitol
Boric acid
Sodium hydroxide (for pH-adjustment)

Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Opened bottle: 4 weeks after first opening the bottle. Do not store above 25^{o}C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) until opened.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Rhokiinsa is supplied sterile in white low density polyethylene bottles (2.5 ml fill) and tips with white polypropylene caps and anti-tamper seals.

Carton containing 1 bottle.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Santen Oy
Niittyhaankatu 20
33720 Tampere
Finland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 16058/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/12/2024

10 DATE OF REVISION OF THE TEXT

10/04/2026