EU Risk Management Plan for Netarsudil and Latanoprost + Netarsudil

RMP v 4.0

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 11-Nov-2025

Date of final sign-off: 28-Nov-2025

Rationale for submitting an updated RMP: Post-authorisation measure MEA 001.6 decision to withdraw post-authorisation safety study (EMA/PAM/0000272898)

Summary of significant changes in this RMP: Removal of post-authorisation safety study (PASS), safety concerns and the additional monitoring status.

QPPV name: Tapio Kerttula

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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Abbreviations

AE	Adverse Event
ALT	Argon Laser Trabeculoplasty
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
BAK	Benzalkonium Chloride
BID	Twice Per Day (Bis in Die)
CAIs	Carbonic Anhydrase Inhibitors
EEA	European Economic Area
EU	European Union
hERG	human Ether-a-go-go-Related Gene
HTG	High Tension Glaucoma
FDA	Food and Drug Administration
INN	International Nonproprietary Name
LLOQ	Lower Limit of Quantification
NOAEL	No Adverse Effect Level
NTG	Normal Tension Glaucoma
RMP	Risk Management Plan
HED	Human Equivalent Dose
IOP	Intraocular Pressure
OAG	Open Angle Glaucoma
OECD	Organisation for Economic Cooperation and Development
OHT	Ocular Hypertension
OSD	Ocular Surface Disease
POAG	Primary Open Angle Glaucoma
PGA	Prostaglandin Analogue
QD	Once Per Day (Quaque Die)
QID	Four times daily
RMP	Risk Management Plan
SLT	Selective Laser Trabeculoplasty
TEAE	Treatment Emergent Adverse Event
USA	United Stated of America

Part I: Product(s) Overview

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module: 11 Nov 2025

Part I Products overview

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
Pharmacotherapeutic group(s) (ATC Code)	Antiglaucoma preparations and miotics ATC code: S01EX05 (Rhokiinsa) ATC code: S01EE51 (Roclanda)
Marketing Authorisation Holder	Santen Oy Niittyhaankatu 20 33720 Tampere Finland
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Rhokiinsa 200 micrograms/ml Eye Drops, Solution (netarsudil) Roclanda 50 micrograms/ml + 200 micrograms/ml Eye Drops, Solution (latanoprost + netarsudil)
Marketing authorisation procedure	Centralised

Brief description of the product	Rhokiinsa contains the single active substance netarsudil. Roclanda contains two active substances, netarsudil and latanoprost, in a fixed combination. Summary information regarding the active substances is provided below. <u>Netarsudil</u> *Chemical class:* Netarsudil is an inhibitor of Rho-associated, coiled coil-containing protein Kinase (Rho Kinase or ROCK). Rho Kinase is a serine/threonine kinase whose activity increases actomyosin contraction in various cell types. Rho Kinase inhibitors represent a new class of ocular hypotensive medications for the treatment of glaucoma, and ocular hypertension. Netarsudil's physiochemical characteristics were engineered specifically for efficient topical ocular delivery. 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 C28H27N3O3 and the molecular formula of the dimesylate is C30H35N3O9S2. <u>Latanoprost</u> Latanoprost is a prostaglandin F2α analogue and a selective prostanoid FP receptor agonist.
	Summary of mode of action: Netarsudil Netarsudil is a Rho Kinase inhibitor for both isoforms of human Rho Kinase (ROCK 1 and ROCK 2) and a norepinephrine transporter (NET) inhibitor. Both of these biochemical activities likely contribute to the multiple mechanisms by which topical netarsudil influences aqueous humor dynamics and lowers intraocular pressure (IOP) in the eye. Studies in animals and humans suggest that the main mechanism of action for IOP lowering is increased outflow through the trabecular meshwork which is achieved by relaxation of trabecular meshwork tissue and reduction of episcleral venous pressure. Rho Kinase inhibitors appear to relax trabecular tissue and dilate blood vessels through their effects on cellular actomyosin dynamics. Latanoprost Latanoprost reduces intraocular pressure by increasing the outflow of aqueous humor. Studies in animals and humans indicate the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.
Hyperlink to the Product Information	Summary of Product Characteristics (SmPC)

Indication(s) in the EEA	*Current* Rhokiinsa: Reduction of elevated intraocular pressure in adult patients with primary open-angle glaucoma or ocular hypertension. Roclanda: Reduction of elevated intraocular pressure in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.
	Proposed (if applicable): N/A
Dosage in the EEA	*Current* Rhokiinsa: One drop in the affected eye(s) once daily in the evening. Roclanda: One drop in the affected eye(s) once daily in the evening
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	*Current* Rhokiinsa: 200 micrograms/ml Eye Drops, Solution (Netarsudil) Roclanda: 50 micrograms/ml + 200 micrograms/ml Eye Drops, Solution (Latanoprost + Netarsudil)
	Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specificationPart II: Module S1 - Epidemiology of the indication(s) and target population(s)

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module | 17 June 2020

Part II: Module S1 - Epidemiology of the indication(s) and target population(s)

Elevated Intraocular Pressure In Adults With Open-Angle Glaucoma and Ocular Hypertension

Open-angle glaucoma (OAG) is a sight-threatening disease in which there is characteristic optic nerve damage or dysfunction (e.g. visual field loss), the anterior chamber angle is open upon gonioscopic observation, and frequently there is elevated intraocular pressure (IOP). A related disease condition is ocular hypertension (OHT) in which patients have elevated IOP compared to a population-based cut-off value, in the absence of apparent optic nerve damage (1). Patients with OHT have an increased risk of developing OAG. Currently, the only modifiable risk factor for glaucomatous visual field loss is IOP.

Incidence and Prevalence:

Glaucoma affects more than 60 million people worldwide (2,3). The mean prevalence is estimated to be 1.96%. The majority of these individuals will have Open-Angle Glaucoma (OAG), estimated 45 million, which is the most common form of glaucoma and almost a quarter (23.9%) of these people are European (4).

Demographics of the population in the proposed indications and risk factors for the disease:

The mean IOP in normal adult populations is estimated at 15-16 mmHg, with a standard deviation of +/- 3.0 mmHg. Traditionally, normal IOP has been defined as two standard deviations above normality, i.e. 21 mmHg, and any IOP above this level is considered to be elevated. The level of IOP is a major risk factor for the development of glaucoma and its progression. For example, the risk of having glaucoma for those with IOP measurements of 26 mmHg or greater is estimated to be 12 times higher than that for those with IOP within the normal range (5).

Older age is also an important factor for progression in glaucoma. IOP slowly rises with increasing age and age of over 40 is considered as a risk factor for the development of ocular hypertension (OHT) and glaucoma (6,5).

The risks of OHT include the development of glaucoma over a period of 5-10 years (7). Other patient characteristics associated with an increased risk for progression of glaucoma include: thinner central corneal thickness in HTG (High Tension Glaucoma); high vertical cup-to-disk ratio; black or African-American race; lower systolic blood pressure in NTG (Normal Tension Glaucoma), and lower ocular perfusion pressures, exfoliation syndrome, more baseline damage and disc haemorrhages (8).

Patients with glaucoma are at the risk of progression of visual loss which potentially may lead to blindness if the condition is not treated appropriately. Patients may also develop optic nerve damage (glaucomatous optic neuropathy including disc haemorrhage; visible nerve fibre layer defects; notching or vertical ovalisation of the cup; asymmetric cupping, especially if >0.7 etc.). Patients with open-angle glaucoma who have a worse mean deviation to their visual field, a greater vertical cup-to-disc ratio at baseline, or who are older, are significantly more likely to experience rapid progression of glaucoma and rapid decay (>36% per annum) of their visual field, according to a study of 767 eyes from 566 participants in the Advanced Glaucoma Intervention Study (9). Other factors associated with an increased risk for progression of glaucoma that did not reach significance are being male and having worse baseline visual acuity.

The main existing treatment options:

The goal of glaucoma treatment is to preserve the patient's visual function and maintain the quality of life. Currently, lowering IOP is the only approach proven to be effective in preserving visual function (5). For patients with OHT, when risk of progression to OAG is present, treatment with IOP-lowering medications is indicated. IOP lowering can be achieved with medications, laser therapy, or incisional glaucoma surgery, with medication being the most common initial intervention. The major drug classes for medical treatment of OAG include the following: miotics, beta-adrenergic receptor antagonists (beta blockers), carbonic anhydrase inhibitors (CAIs), alpha-adrenergic receptor agonists (alpha agonists), and prostaglandin analogues (PGAs). The pharmacodynamic effects of these medications can differ substantially as some affect aqueous humor production (beta blockers, alpha-agonists, and CAIs) while others affect aqueous

humor outflow (miotics, PGAs, and alpha-agonists) (European Glaucoma Society 2014). In EU, no commonly used agent acts primarily to increase outflow via a direct effect on the trabecular outflow pathway, the site of the pathology that causes elevated IOP.

The medications currently available for glaucoma treatment have different limitations and risks, therefore the treatment must be tailored to an individual patient's needs and preferences. Some therapeutic classes have known systemic adverse effects, for example beta-adrenergic antagonists (with cardiovascular and respiratory effects such as bradycardia, dyspnea, and wheezing) and alpha-agonists (with nervous system effects such as dry mouth, fatigue, sedation, and dizziness). Ocular side effects are common with topical agents and the acceptability of different side effects can vary by patient. Therefore, additional therapeutic options for individualizing glaucoma treatment will be beneficial for both clinicians and patients. As with all interventions, the risks of treatment should be outweighed by the benefits. The risks of the disease will be different for the patients who have only elevated IOP and no other symptoms (OHT) than for OAG patients who have sustained damage to the optic nerve, or patients who have demonstrated recent continuing elevation of IOP on successive visits (10).

Laser treatment and minimally invasive glaucoma surgery may be considered as initial therapy in selected glaucoma patients. Conventional surgical therapy is not viewed as a first-choice treatment for OAG and OHT and is usually indicated when glaucomatous optic neuropathy worsens and the patient is on maximum tolerated medical therapy (10).

Natural history of the indicated condition in the population, including mortality and morbidity:

Glaucoma, if left untreated, can cause significant visual loss, and may eventually lead to irreversible blindness and significantly impact quality of life. Progression of glaucoma is the main source of ocular morbidity. The early manifest glaucoma trial (EMGT) demonstrated that a 25% reduction of IOP from baseline reduced the risk of glaucoma progression by 50% (11). In addition, with each mmHg IOP reduction from baseline, the risk of glaucoma progression decreased 10%. The ocular hypertension treatment study (OHTS) similarly showed a 50% reduction of risk in the treatment group compared with the untreated group (5,12).

Important co-morbidities:

Other co-morbidities expected in the target population are the most common pre-existing disorders for the ageing population, including hypertension, hyperlipidemia, diabetes and stroke.

Part II: Module SII - Non-clinical part of the safety specification

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Data lock point for this module | 17 June 2020

Part II: Module SII - Non-clinical part of the safety specification

Information in this section focuses on nonclinical data generated with netarsudil as a new active substance, in line with guidance in Section V.C.1.1.4 of GVP Module V (Revision 2). Relevant data generated with the combination of netarsudil and latanoprost is also included.

Netarsudil was studied in a series of pharmacology, pharmacokinetics, toxicokinetics and toxicology studies in relevant species: Dutch Belted rabbits and cynomolgus monkeys for topical studies, rats and dogs for systemic toxicology studies, and rats and New Zealand White rabbits for embryo-fetal studies.

All of the topical ophthalmic safety studies were performed with the same formulation and similar bottle container/closure configuration as is intended for the commercial product.

Key safety findings from non-clinical studies:

Netarsudil has been evaluated in a package of non-clinical pharmacology, safety pharmacology, pharmacokinetic, general toxicity and toxicokinetics, genotoxicity and reproductive and developmental toxicology studies using ocular (clinical route) and parenteral (intravenous) administration. All of the topical ophthalmic safety studies were performed with the same formulation and similar bottle container/closure configuration as is intended for the commercial product. Where appropriate, non-clinical safety studies were conducted in compliance with the requirements of The Organisation for Economic Cooperation and Development (OECD) Good Laboratory Practice (GLP) Regulations. Standard laboratory species and strains were used for safety studies based on the wide distribution of the target enzyme, Rho Kinase, throughout the animal kingdom (13) and in vitro metabolism studies which indicated a common metabolic route for netarsudil in rat, rabbit, dog, primate and human. Topical ocular studies and autoradiography assessments were conducted in pigmented and partially pigmented animals, respectively, due to the binding affinity of netarsudil and its active metabolite to melanin.

Pharmacology

Netarsudil mesylate is a potent Rho kinase inhibitor (14,15). Published studies indicate that inhibition of Rho kinase causes rapid and reversible disassembly of actin stress fibers and focal adhesions in many non-muscle cell types including porcine, bovine and human trabecular meshwork cells (16). Inhibition of Rho kinase by netarsudil in the anterior chamber of the eye has been shown to cause expansion (relaxation) of the trabecular meshwork, which decreases resistance to conventional outflow, resulting in a lowering of IOP. Following topical application to the eye, netarsudil mesylate is metabolized by corneal esterases to a metabolite (AR-13503) which is approximately 5 times more potent than the parent compound.

Netarsudil mesylate may lower IOP through multiple mechanisms of action. An ex vivo study in human eye anterior segments showed that AR-13503 increased outflow through the human trabecular outflow pathway, with correlated morphological changes including an increase in the area of actively filtering trabecular meshwork tissue, expansion of the trabecular meshwork tissue, and dilation of episcleral veins (AR-13324-IPH05). IOP-lowering activity has been demonstrated in primary pharmacodynamic studies in normotensive Dutch Belted rabbits (AR 13324-APH01, AR-13324-APH03, AR 13324 APH04, AR 13324 APH05, PG324 APH01) and Formosan Rock monkeys (AR 13324 APH06, AR-13324-APH02) in which netarsudil mesylate produced large reductions in IOP that were maintained for 24 hours after once-daily (QD) topical ocular dosing at concentrations of 0.01%, 0.02% and 0.04%. In rabbits, reduced Episcleral Venous Pressure (EVP) was observed, which is expected to contribute to the lowering of IOP by increasing outflow through the trabecular outflow pathway. In monkeys, topical ocular administration of netarsudil ophthalmic solution lowered IOP by increasing aqueous humor outflow through the trabecular meshwork and decreasing the production of aqueous humor. Netarsudil mesylate also showed inhibitory activity against monoamine reuptake receptors, including the norepinephrine transporter (NET) which may be responsible for the reduction in aqueous humor production that occurs upon topical ocular administration of netarsudil ophthalmic solution in monkeys.

The IOP-lowering efficacy of netarsudil and latanoprost in combination was also demonstrated in a 3-day study in normotensive Formosan Rock monkeys (PG324-APH02).

Safety Pharmacology

Complete competitive binding of the human ether a-go-go related gene (hERG) potassium channel was noted in an in vitro ligand binding assay with netarsudil mesylate at a test concentration of 10 µM (AR 13324-IPH03). This concentration is at least 1000-fold higher than the maximum theoretical blood concentration of netarsudil which may occur in patients following bilateral topical ocular administration (based on LLOQ of 0.100 ng/mL). The single enantiomer active metabolite of netarsudil mesylate, AR 13503, was not tested, but the racemate of the metabolite exhibited no significant binding activity for the hERG potassium channel. Netarsudil mesylate showed significant inhibition of hERG current in a standard assay using voltage clamped human embryonic kidney cells (HEK293), with an IC50 value of 0.4 µM (181 ng/mL, based on a molecular weight of 453.54 g/mole) (AR-13324-IS03). However, netarsudil mesylate showed complete binding to rat, dog and human plasma proteins when tested in vitro at concentrations of 10 µM, 100 µM and 1 mM (AR-13324-IPK01). Hence, even at micromolar concentrations, the amount of free netarsudil available to interact with appropriate receptor targets will be greatly reduced due to plasma protein binding. The metabolite AR-13503 showed lower plasma protein binding over the same concentration range: 48% to 50% in rats, 42% to 45% in dogs and 61% to 71% in humans.

Intravenous administration of netarsudil mesylate on cardiovascular parameters in conscious telemetered dogs showed no effect on cardiac or circulatory functions at 1 mg/kg (corresponding to plasma exposure of 26.6 ng/mL at 30 minutes post-dose), but decreased arterial pressure and increased heart rate were noted at 12.5 and 25 mg/kg (plasma exposures of 412.3 ng/mL and 871.7 ng/mL, respectively, at 30 minutes post-dose), with clinical signs of vasodilation being observed at 25 mg/kg (AR-13324-AS08). None of the doses tested had any toxicological effects on cardiac rhythm or ECG morphology, or in quantitative measures, including QTc interval. Rho kinase inhibitors are known to reduce blood pressure by decreasing vascular wall smooth muscle contractility and thereby reducing vascular tone (17,18,19). No notable effects on ECG measurements were reported in the 7-day or 28-day repeated intravenous dose toxicity studies in the dog using doses up to 6 and 1 mg/kg, respectively.

As part of the 7-day intravenous repeat dose toxicity study in rats (AR-13324-AS03), a functional observational battery was performed. The battery was performed prior to treatment initiation and at 30 ± 15 minutes following dose administration on Days 1 and 7 of the dosing phase and included, among others, observations for effects on respiration, motor activity, abnormal posture, excretion, piloerection, pupil size, corneal reflex, body temperature, awareness reaction, body tremors, immobility, ataxia, stereotypy and loss of righting. There were no treatment related findings observed in any of the dose groups, including no decrease in respiration. The highest dose tested was 10 mg/kg/day, which is approximately 1,600 times the clinical exposure following ocular instillation to humans.

Pharmacokinetics

Ocular and systemic tissue distribution studies indicate that radioactivity observed in tissues is cleared relatively quickly from the body (e.g. T1/2 of 12 to 27 hours for ocular tissues, blood, plasma, liver and kidney), suggesting that there is no long-lasting systemic tissue exposure to the drug or its metabolite by either route of administration (AR-13324-AS05; AR-13324-AS15; AR 13324-AS11; AR 13324 AS13; AR 13324-AS06; AR-13324-AS07; AR-13324-AS12; AR 13324-AS14; AR 13324 APK03; AR 13324 APK04). There was no evidence that netarsudil racemized in vivo.

Relative ocular tissue distributions were the same for netarsudil and latanoprost whether they were administered separately or as part of a fixed dose combination formulation as a single topical ocular dose in Dutch-Belted Rabbits (PG324-APK01).

Toxicology

In the rat and dog 7-day repeated intravenous dose studies with netarsudil mesylate, red skin consistent with vasodilation was noted on various body surfaces at doses of 1 mg/kg/day or higher (AR-13324-AS03, AR-13324-AS04). The corresponding plasma exposures on Day 7 were: Rat C_{max} of 15.1 (M) and 13.6 (F) ng/mL and $AUC_{0\text{-}inf}$ of 60.2 (M) and 51.4 (F) ng.hr/mL; Dog C_{max} of 45.2 (M) and 40.1 (F) ng/mL and $AUC_{0\text{-}inf}$ of 306.0 (M) and 382.0 (F) ng.hr/mL. In the rat (AR-13324-AS09) and dog (AR-13324-AS10) 28-day repeated-dose studies, the No Observed Adverse Effect Level (NOAEL) was 1 mg netarsudil mesylate/kg/day (the highest dose tested). The corresponding plasma exposures on Day 1 [and 28] were: Rat C_{max} of 64.9 [64.5] (M) and 59.4 [57.0] (F) ng/mL and $AUC_{0\text{-}24h}$ of 130.8 [125.8] (M) and 138.7 [121.5] (F) ng.hr/mL; Dog C_{max} of 52.7 [63.3] (M) and 41.8 [51.5] (F) ng/mL and $AUC_{0\text{-}24h}$ of 281.6 [481.7] (M) and 209.2 [334.8] (F) ng.hr/mL. Human Equivalent Doses (HED) are 9.6 mg/day based on the rat NOAEL

and 33 mg/day based on the dog NOAEL. These HED levels are ~700 to ~2350 times higher than the recommended human dose of 0.014 mg/day (netarsudil ophthalmic solution 0.02% dosed QD in both eyes). Furthermore, the plasma exposures at the NOAELs following intravenous administration in the rat and dog are more than 400 times greater than the potential worst-case plasma exposure in humans following topical ocular administration of netarsudil ophthalmic solution during clinical use (reported to be < 0.100 ng/mL).

Local effects of netarsudil ophthalmic solution following QD ocular application in the rabbit at up to 0.08% for 7 days were limited to sporadic observations of minor irritation with minimal intensity (AR 13324-AS05). The NOAEL was 0.08% QD. However, QID ocular dosing in the rabbit (up to 0.04%) and monkey (up to 0.12%) for 7 days (AR 13324-AS05; AR-13324-AS06, AR-13324-AS07) showed gross and ophthalmic signs of irritation (corneal staining and edema, and histopathologic indications of inflammation [hypertrophy and hyperplasia of the corneal epithelium, edema of the corneal stroma and/or corneal epithelium, and increased apoptosis of the corneal endothelium]). Findings lessened in severity and incidence as dosing progressed and resolved after a post-dose recovery period. However, both 0.04% and 0.12% netarsudil ophthalmic solution QID for 7 days in the monkey showed findings of vitreal haze, optic disc hyperemia and/or retinal edema, possibly related to hypotony resulting from the >70% reduction in IOP in these animals. No NOAEL was established following QID dosing in the rabbit (NOAEL < 0.04%). The NOAEL in the monkey was 0.01% netarsudil QID (2-times higher than the recommended human dose of netarsudil ophthalmic solution 0.02% QD). In longer duration topical ocular administration studies in the rabbit (up to 6 months, AR-13324-AS13) and monkey (up to 9 months, AR-13324-AS14), use of lower doses and less frequent dosing regimens (BID) resulted in findings of mild ocular irritation which appeared early in the studies and decreased in severity with continued dosing. The NOAELs for local effects were 0.02% netarsudil ophthalmic solution BID for 6 months in the rabbit (2-times higher than proposed human dose) and 0.04% netarsudil ophthalmic solution BID for 9 months in the monkey (4-times higher than proposed human dose).

The ocular toxicity of netarsudil and latanoprost in a fixed-dose-combination formulation when administered QD or BID by topical ocular dosing OU for 3 months was investigated in Dutch-Belted rabbits (PG324-AS01). There was no overt systemic toxicity observed. Minor ocular irritation, but no test article related ocular lesions, was observed. The NOAEL was the highest dose tested – netarsudil/latanoprost 0.02%/0.005% dosed BID (2 times higher than proposed human dose).

Intravenous administration (via central venous catheter) embryofetal studies in rats (up to 3 mg/kg/day on Gestation Days [GD] 6 to 17) and New Zealand White rabbits (up to 5 mg/kg/day, GD 6 to 19) reported increased numbers of spontaneous abortions, decreased uterus and body weights, decreased numbers of viable fetuses, increased numbers of resorptions and post-implantation losses at the higher dose levels (AR-13324-AS21; AR-13324-AS22). Netarsudil mesylate did not induce malformations or variations in fetal external, soft, or skeletal tissues. The NOAEL for embryofetal toxicity was 0.1 mg/kg/day in rats (corresponding to netarsudil plasma C_{max} ~4 ng/mL, AUC0-24¬ ~3.4 ng.h/mL) and 3 mg/kg/day in rabbits (netarsudil C_{max} 133 ng/mL, AUC0-24¬ 165 ng.h/mL; metabolite AR-13503 C_{max} 47.5 ng/mL, AUC0-24 65.4 ng.h/mL) (AR-13324-AS21; AR-13324-AS22). These rat and rabbit netarsudil plasma exposures at the NOAELs represent a minimum of 40-times and 1330-times the expected human exposure, respectively, based on C_{gf}, and a similar or greater margin based on AUC0-24 (human plasma concentrations of netarsudil and AR-13503 were below the LLOQ of 0.100 ng/mL after dosing netarsudil ophthalmic solution 0.02% QD in a Phase I clinical PK study). Netarsudil mesylate has not been assessed in nonclinical studies for potential effects on fertility or pre- and post-natal development, due to the limited systemic exposure following topical ocular administration. Juvenile toxicity studies have not been performed and are not planned.

An appropriately conducted package of genotoxicity studies, comprising an in vitro bacterial reverse mutation assay (AR-13324-IS01), an in vitro mammalian cell gene mutation test (AR 13324-IS02), and an in vivo micronucleus test (7-day intravenous administration at 10 mg/kg, AR-13324-AS03) showed no evidence of genotoxicity of netarsudil mesylate. No carcinogenicity studies have been conducted with netarsudil mesylate based on a lack of detectable systemic exposure following ocular topical administration and no cause for concern identified from the package of genotoxicity studies (no genotoxic effects), mass balance studies in pigmented rats (no evidence of long-term retention of parent compound or metabolite), and chronic repeated topical ocular administration studies in the rabbit and monkey (no findings of pre neoplastic lesions).

Netarsudil tested negative in a well-established in vitro neutral red uptake phototoxicity assay in BALB/c 3T3 Mouse fibroblasts (AR-13324-IS04). 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 (AR-13324-IS05).

Summary of key non-clinical safety findings and relevance to human usage:

Based on *intravenous* dosing in the non-pregnant rat and dog and the pregnant rat and rabbit, notable safety findings comprised effects on the cardiovascular system (known class pharmacological effects of Rho kinase inhibitors) and toxicity to embryofetal development. However, NOAELs were established in these studies with corresponding plasma exposures which were significantly higher than the anticipated human systemic exposure following proposed ocular topical administration in clinical use (human plasma levels <0.100 ng/mL for both netarsudil mesylate and the active metabolite):

Nonclinical study type	**Endpoint and exposure concentration**	**Comparison to anticipated human systemic exposure following ocular topical administration**
hERG assay (*in vitro*)	IC_{50} 0.4 µM (=181 ng/mL)	>1810 times higher than human exposure level
Cardiovascular Safety Pharmacology study in dog	NOAEL = 1 mg/kg/day ($C_{30\ minutes}$ = 26.6 ng/mL	>266 times higher than human exposure level
General toxicity (rat, 28 day repeated i.v. dosing)	NOAEL = 1 mg/kg/day (C_{max} of 57 to 64.9 ng/mL AUC_{0-24h} of 121.5 to 138.7 ng.h/mL	>570 times higher than human exposure level
General toxicity (dog, 28 day repeated i.v. dosing)	NOAEL = 1 mg/kg/day (C_{max} of 41.8 to 63.3 ng/mL and AUC_{0-24h} of 209.2 to 481.7 ng.h/mL	>418 times higher than human exposure level
Embryofetal development (rat, repeated i.v. dosing)	NOAEL = 0.1 mg/kg/day (C_{max} ~4 ng/mL)	~ 40 times higher than human exposure level
Embryofetal development (rabbit, repeated i.v. dosing)	NOAEL = 3 mg/kg/day (C_{max} = 133 ng/mL [parent] and 47.5 ng/mL [metabolite]	>1330-times higher parent and >475-times higher metabolite exposure than human exposure levels

Hence, the relatively high plasma exposure levels seen at the NOAELs in nonclinical studies indicate no cause for concern for systemic effects of netarsudil ophthalmic solution 0.02%, following once-daily ocular topical administration in humans.

Ocular administration studies in the rabbit and monkey indicate potential local site irritation which was noted in the pivotal chronic rabbit (6 month) and monkey (9 month) studies at doses that reflect at least twice the anticipated human daily dose, and in the 28-day repeated dose ocular studies, following twice daily (BID) dosing in these species at up to 0.06% concentration of netarsudil ophthalmic solution (the highest dose administered in these studies, corresponding to 6-times the proposed human dose).

Corneal haze was noted in the monkey following topical ocular dosing, which may be related to the findings of "corneal deposits" and "corneal verticillata" associated with netarsudil ophthalmic solution 0.02% treatment in Phase III clinical studies. Drug induced corneal verticillata or "lipid microdeposits" are commonly seen in patients on amiodarone therapy (20,21) and arise from phospholipidosis (accumulation of phospholipids in lysosomes). In a tissue culture assay, netarsudil mesylate showed drug-induced phospholipidosis with an EC50 value of 1.1 µM (corresponding to 497.75 ng/mL), which is a physiological concentration for netarsudil in the cornea, based upon rabbit ocular PK studies (AR 13324 APK03). However, the active metabolite AR-13503, which predominates in the aqueous humor after topical dosing in rabbits, did not induce phospholipidosis in this assay. Together, these data suggest that netarsudil concentrations in the cornea are high enough to potentially induce phospholipidosis, but are too low in the aqueous humor (<0.2 nM; <90.5 ng/mL) to induce phospholipidosis in intraocular tissues. If corneal haze in monkeys is due to phospholipidosis, it is noteworthy that the timing with which it arose and resolved

was faster than was seen in the Phase III studies. In the monkey 9-month ocular safety study, corneal haze arose within the first week of dosing, typically persisted through the 3-month time point, and then resolved during the remaining 6 months of dosing for all but 1 animal, which resolved during the 4-week recovery period.

In clinical trials, corneal deposits were not observed in the 28-day Phase II studies and were first detected in the Phase III studies after 6 weeks of dosing. In the 12-month Phase III study, some patients with corneal deposits resolved with continued dosing, but for most patients remaining in the study for 12 months, the finding persisted until the end of the dosing period. An observational study, AR-13324-OBS01, of subjects who developed corneal deposits in a Phase III trial (AR-13324-CS302) was conducted to assess changes in corneal deposits over time in 45 subjects. At the completion of this observational study, cornea verticillata resolved in all subjects except for 3 subjects (4 out of the 6 eyes) where cornea verticillata remained stabilized but unresolved. After study completion, cornea verticillata resolved in 1 of these subjects and had improved in the other 2 subjects (3 out of 4 eyes). There was no clinically meaningful change in the visual function assessments (visual acuity, contrast sensitivity, and visual function (VF)-14 questionnaire) when comparing baseline results with cornea verticillata present to results obtained after resolution/stabilization of the cornea verticillata.

Part II: Module SIII - Clinical trial exposure

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module | 17 June 2020

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

Information in this section focuses on clinical data generated with netarsudil as a new active substance, in line with guidance in Section V.C.1.1.4 of GVP Module V (Revision 2). Relevant data generated with the combination of netarsudil and latanoprost is also included.

The original development program conducted in support of netarsudil ophthalmic solution 0.02% comprises ten completed clinical studies (Phases I to III).

The Phase I studies included two prospective studies on healthy subjects with treatment with 0.02% netarsudil once daily (QD). Three Phase II, prospective, randomised, double masked, studies included dosing with varying concentrations of netarsudil 0.01%, 0.02% and 0.04% QD. Four Phase III, prospective, randomised, double masked, studies included dosing with netarsudil 0.02% QD (in all 4 studies) and BID (in 2 studies).

There were an additional three studies which were designed to investigate a fixed dose combination of netarsudil/latanoprost as part of a separate development program; these also included a netarsudil 0.02% QD treatment arm. These studies, all prospective, randomised, double-masked, included one Phase II and two Phase III studies. Data from these studies inform the safety profile of netarsudil as both a single agent and in a fixed combination with latanoprost.

SIII.2 Clinical trial exposure

Overall, a total of 4082 subjects were treated with therapy (netarsudil, netarsudil/latanoprost, and comparators) in completed trials, which included 1834 subjects receiving 0.02% netarsudil (QD: 1545 and BID: 289) and 555 subjects receiving netarsudil/latanoprost 0.02%/0.005%. A total of 1950 subjects were treated with netarsudil ophthalmic solution (0.01%, 0.02% (QD/BID) or 0.04%) in the twelve completed studies across both the monotherapy and the fixed dose combination product development programs; including 29 healthy subjects in Phase I studies, 295 subjects in Phase II studies and 1626 subjects in Phase III studies. A total of 628 subjects were treated with netarsudil/latanoprost in the three completed studies with the fixed dose combination, including 146 in Phase II studies and 482 in Phase III studies.

In addition to the interventional studies described above, a non-interventional Cornea Verticillata Observational Study (AR-13324-OBS01) has been completed to evaluate visual function (e.g., visual acuity, contrast sensitivity, VF-14 Questionnaire) and corneal deposit grading in subjects who developed cornea verticillata or corneal opacity while participating in study AR 13324 CS302. As the study was non-interventional, it has not been included in the exposure information outlined in this section.

The evaluation of safety was conducted on all subjects who were enrolled into a study and received at least one dose of study drug. The safety parameters analysed in these studies provided a comprehensive assessment of the ocular and systemic safety of netarsudil ophthalmic solution 0.02%. The safety assessments conducted in the completed studies included the following: extent of exposure; adverse events; and other ocular and systemic safety-related assessments.

Ocular safety-related assessments included visual acuity, IOP, slit-lamp biomicroscopy parameters (eyelid, conjunctiva, cornea, anterior chamber, iris/pupil, lens), ophthalmoscopy parameters (choroid, macula, optic nerve, retina, vitreous, cup-disc ratio), ocular comfort assessment, visual field, pachymetry, pupil size, and specular microscopy. Systemic safety assessments included vital signs (heart rate and blood pressure) and clinical laboratory testing (haematology and blood chemistry).

The most relevant safety information was obtained in the Phase II and III studies since these studies were randomized, double-masked, and active or vehicle-controlled and conducted in the patient population (OAG and OHT) for which the product is intended, whereas the Phase I studies were conducted in healthy subjects. Thus, the description of safety will focus primarily on the Phase II and Phase III studies. Pooled analyses were also performed on the four Phase III studies part of the netarsudil ophthalmic solution 0.02%

development program and, separately, on the two Phase III studies part of the netarsudil/latanoprost 0.02%/0.005% development program; these data are also presented where applicable.

An overview of subject exposure to the monotherapy product netarsudil ophthalmic solution 0.02% and the fixed dose combination product netarsudil/latanoprost ophthalmic solution 0.02%/0.005% by duration and dose level across all interventional studies completed in both development programs is included in respective **Table SIII *1*** and **Table SIII *2*** below. Subject demographics by age, gender, race and iris colour for subjects included in Phase II and III studies conducted as part of both development programs are presented in **Table SIII *3*** - **Table SIII *10***.

Table SIII 1 Duration of exposure and dose (Rhokiinsa development program)

Cumulative for indication	
Duration of exposure	Patients
0 to <3 m	684
0.01% QD	97
0.02% QD	457
0.02% BID	111
0.04% QD	19
≥3 to <6 m	532
0.01% QD	0
0.02% QD	475
0.02% BID	57
0.04% QD	0
≥6 m to <12m	395
0.01% QD	0
0.02% QD	361
0.02% BID	34
0.04% QD	0
≥12m	339
0.01% QD	0
0.02% QD	252
0.02% BID	87
0.04% QD	0

Source: Rhokiinsa 2.7.4 Table 7: Duration of Exposure to Study Drug by Treatment Group (All completed studies across original netarsudil 0.02% and netarsudil/latanoprost 0.02%/0.005% ophthalmic solution programs)

Table SIII 2 Duration of exposure and dose (Roclanda development program)

Cumulative for indication	
Duration of exposure	Patients
0 to <3 m	157
0.01% QD	73
0.02% QD	84
≥3 to <6 m	221
0.01% QD	0
0.02% QD	221
≥6 m to <12m	66

Cumulative for indication	
0.01% QD	0
0.02% QD	66
≥12m	111
0.01% QD	0
0.02% QD	111

NOTE: The concentration of latanoprost in the netarsudil/latanoprost component was 0.005% for both netarsudil concentrations; Source: Roclanda 2.7.4 Table 7 and Rhokiinsa ISS Table 14.3.12.9.1.98

Table SIII 3 Age group (Rhokiinsa) – Netarsudil 0.02% QD

Age	Patients
< 18 years	1
18 – 64 years	432
65 – 74 years	352
75 – 84 years	167
≥85 years	17

Source: Rhokiinsa ISS Table 14.3.3.3.3.6.99 (post-hoc) Number and Percentage of Subjects for Netarsudil 0.02% QD by Age Group; AR-13324-CS206 Listing 16.2.4.1

Table SIII 4 Age group (Roclanda) – Netarsudil/Latanoprost 0.02%/0.005%

Age	Patients
< 18 years	0
18 – 64 years	262
65 – 74 years	194
75 – 84 years	90
≥85 years	10

Source: Roclanda 2.7.4 Table 10 Number and Percentage of Subjects for Netarsudil/Latanoprost 0.02%/0.005% by Age Group

Table SIII 5 Gender (Rhokiinsa)

Gender	Patients[1]
Male	544 (387)
Female	801 (553)

Source: Rhokiinsa 2.7.4 Table 8 9 Demographics of Subjects in Phase II and Phase III Clinical Studies in Netarsudil Ophthalmic Solution 0.02% Development Program
[1] All netarsudil treatment groups; numbers in parentheses are for patients treated with the indicated dose netarsudil 0.02% QD

Table SIII 6 Gender (Roclanda)

Gender	Patients[1]
Male	258 (231)
Female	372 (325)

Source: Roclanda 2.7.4 Table 9 Demographics of Subjects in Clinical Studies
[1] All netarsudil/latanoprost treatment groups; numbers in parentheses are for patients treated with the indicated dose netarsudil/latanoprost 0.02%/0.005% QD

Table SIII 7 Ethnic origin (Rhokiinsa)

Race	Patients[1]
Native American	2 (2)
Asian	24 (14)
Black or African American	314 (224)
White	1001 (697)
Other	4 (3)

Source: Rhokiinsa 2.7.4 Table 8 and Table 9 Demographics of Subjects in Phase II and Phase III Clinical Studies in Netarsudil Ophthalmic Solution 0.02% Development Program
[1] All netarsudil treatment groups; numbers in parentheses are for patients treated with the indicated dose netarsudil 0.02% QD

Table SIII 8 Ethnic origin (Roclanda)

Race	Patients[1]
Native American	0
Asian	18 (15)
Black or African American	168 (153)
White	441 (385)
Other/Multiple	3

Source: Roclanda 2.7.4 Table 9 Demographics of Subjects in Clinical Studies
[1] All netarsudil/latanoprost treatment groups; numbers in parentheses are for patients treated with the indicated dose netarsudil/latanoprost 0.02%/0.005% QD

Table SIII 9 Iris Colour (Rhokiinsa)

Iris Colour	Patients[1]
Blue/Grey/Green	351 (240)
Brown/Black	835 (588)
Hazel	157 (110)
Other	2

Source: Rhokiinsa 2.7.4 Table 8 and Table 9 Demographics of Subjects in Phase II and Phase III Clinical Studies in Netarsudil Ophthalmic Solution 0.02% Development Program
[1] All netarsudil treatment groups; numbers in parentheses are for patients treated with the indicated dose netarsudil 0.02% QD

Table SIII 10 Iris Colour (Roclanda)

Iris Colour	Patients[1]
Blue/Grey/Green	162 (141)
Brown/Black	399 (352)
Hazel	69 (63)
Other	0

Source: Roclanda 2.7.4 Table 9 Demographics of Subjects in Clinical Studies
[1] All netarsudil/latanoprost treatment groups; numbers in parentheses are for patients treated with the indicated dose netarsudil/latanoprost 0.02%/0.005% QD

Common Adverse Events (AEs):

Phase I Studies: In the Phase I studies in healthy volunteers, chronologically conducted after the Phase II studies, nearly every subject experienced conjunctival hyperaemia during treatment with netarsudil 0.02% dosed QD AM. The majority of the conjunctival hyperaemia AEs were mild in severity. A small number of other ocular adverse events were also noted including eye pruritus, visual impairment, dry eye, vital dye staining cornea present and headache. No AEs resulted in discontinuation of the study drug.

Phase II Studies: In the Phase II studies, in the netarsudil treatment groups, the most frequently reported ocular adverse event was conjunctival hyperaemia. The majority of the conjunctival hyperaemia AEs were mild in severity. Non-ocular AEs were rarely reported. The most frequently reported non-ocular AEs across all treatment groups included headache and nasopharyngitis.

Results in the netarsudil/latanoprost treatment groups in the Phase II study conducted with netarsudil/latanoprost were similar. The most frequently reported non-ocular AEs in the netarsudil/latanoprost groups included bronchitis, muscle contractions involuntary and nasopharyngitis.

Phase III Studies: In the four Phase III studies conducted as part of the netarsudil ophthalmic solution 0.02% development program, the most frequently reported ocular AEs in the netarsudil treatment groups were conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage. The incidence of these AEs was lower in the shorter duration studies than in the longer duration studies. Cornea verticillata occurred at a higher incidence in the longer 6 (AR 13324-CS304) and 12-month (AR 13324 CS302, AR 13324-CS303) studies compared to the 3 month study (AR-13324-CS301). Other ocular AEs included: instillation site pain, vision blurred and instillation site erythema.

In the pooled population, the most common ocular adverse events were conjunctival hyperaemia, cornea verticillata, conjunctival haemorrhage, vision blurred, lacrimation increased, erythema of eyelid, visual acuity reduced, eye pruritus, conjunctival oedema, eye irritation, eyelid oedema, foreign body sensation in eyes, corneal opacity, instillation site pain, instillation site erythema, and vital dye staining cornea present. The most frequently reported non-ocular AEs included headache and upper respiratory infection. Treatment-related non-ocular AEs were minimal. For the pooled analyses, the most frequently reported non-ocular AEs included upper respiratory infection, headache and dermatitis allergic.

Results in the netarsudil/latanoprost treatment groups in the pooled Phase III studies conducted with netarsudil/latanoprost were similar. For the pooled analyses, the most frequently reported non-ocular AEs included nasopharyngitis, headache and dermatitis contact.

Part II: Module SIV - Populations not studied in clinical trials

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module | 17 June 2020

Part II: Module SIV - Populations not studied in clinical trials

Patients with hepatic impairment, renal impairment, cardiovascular impairment, immunocompromised patients, pregnant and breastfeeding women, and patients with advanced OAG and OHT were not included in the clinical trials.

The safety of netarsudil or netarsudil/latanoprost in the paediatric population has not been established, and the European Medicines Agency has waived the obligation to submit the results of studies with netarsudil or netarsudil/latanoprost in all subsets of the paediatric population for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. A copy of the paediatric waiver is included in Section 1.10 of the dossier.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

In general, the exclusion criteria for the trials were designed to exclude individuals with coexisting ocular or systemic conditions which would place them at additional risk in the trials, individuals for whom the use of the test or control article was contraindicated, as well as individuals with ocular or systemic conditions or those using ocular or systemic medications that would confound the study results and interfere with the assessment of safety and/or efficacy.

Criterion: Ocular Medication

Subjects were not eligible for enrolment if they used more than two ocular hypotensive medications within 30 days of screening, and fixed dose combinations counted as two medications. Subjects were to be excluded from participation if they used ocular medications of any kind within 30 days of screening with the exception of:

a) Ocular hypotensive medications, which were to be washed out according to the schedule;

b) Lid scrubs, which were allowed prior to screening (prior to dosing for study AR-13324-CS201); or

c) Lubricating drops for dry eye, which were permitted throughout the study.

Reason for exclusion: Using three or more glaucoma medications is an indicator of advanced glaucoma. The clinical trials all required a wash out period in which no IOP lowering eye drops could be used; stopping treatment of advanced glaucoma can place patients at risk for glaucoma progression. Using other ocular medications can interfere with the assessment of safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: This group was excluded from the clinical trials for protection of human subjects and data integrity, it does not represent missing information.

Criterion: Corneal Thickness, previous refractive surgery, or any abnormality preventing reliable IOP measurement

All studies specified that eligible subjects could not have central corneal thickness greater than 600 to 620 µm, since normal corneal thickness typically ranges from 427 to 620 µm (Wolfs 1997), and higher corneal thickness could potentially impact the IOP measurement.

Reason for exclusion: Corneal thickness, previous refractive surgery, or other abnormality of the eye (e.g., keratoconus) can affect IOP reading and confound the efficacy results.

Is it considered to be included as missing information?: No

Rationale: This group was excluded from the clinical trials for data integrity and does not represent missing information.

Criterion: Glaucomatous Damage

Subjects were to be excluded if they had glaucomatous damage so severe that washout of ocular hypotensive medications for one month was not judged safe (e.g., advanced glaucomatous optic nerve head cupping or visual field loss).

Reason for exclusion: Stopping treatment during washout may place patients at risk for glaucoma progression.

Is it considered to be included as missing information?: No

Rationale: This group was excluded from the clinical trials for protection of human subjects and data integrity, it does not represent missing information.

Criterion: Previous glaucoma Intraocular surgery

Subjects were to be excluded if they had glaucoma intraocular surgery, including Selective Laser Trabeculoplasty (SLT) or Argon Laser Trabeculoplasty (ALT)

Reason for exclusion: Having glaucoma intraocular surgery often indicates that patients have advanced glaucoma and executing washout may place patients at risk for glaucoma progression. In addition, previous surgical treatment that targeted the trabecular meshwork (SLT, ALT, trabeculectomy, etc.) could interfere with the assessment of safety and efficacy, since netarsudil also targets the trabecular meshwork.

Is it considered to be included as missing information?: No

Rationale: This group was excluded from the clinical trials for protection of human subjects and data integrity, it does not represent missing information.

Criterion: Other Ocular Pathologies

Trials were designed to exclude individuals with coexisting ocular or systemic conditions placing them at additional risk from participation in the trials, individuals for whom the use of the test or control article was contraindicated, as well as individuals with ocular or systemic conditions or those using ocular or systemic medications that would interfere with the assessment of safety and/or efficacy.

Reason for exclusion: Other ocular conditions or treatment, if required during the clinical trial, could affect the assessment of safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: This group was excluded from the clinical trials for protection of human subjects and data integrity, it does not represent missing information.

Criterion: Abnormal Laboratory Tests

In all of the studies, laboratory tests were reviewed to assess subject eligibility prior to randomization. All protocols contained an exclusion criterion indicating that any clinically relevant abnormalities in laboratory tests at screening that would impact the study would exclude subject participation in the study

Reason for exclusion: Systemic disease or treatment, if required during the clinical trial, may affect the assessment of safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: This group was excluded from the clinical trials for data integrity and does not represent missing information.

Criterion: Pregnancy and Lactation

There are no adequate or well-controlled studies using netarsudil in pregnant women. The clinical studies conducted excluded women of childbearing potential who were pregnant, nursing or not using a medically acceptable form of birth control. Non-clinical studies of embryo-foetal effects indicated netarsudil is

embryotoxic and foetotoxic. However, netarsudil does not cause foetal abnormalities at plasma exposure levels which are 40 times higher (rat) and 1330 times higher (rabbit) than the human plasma concentration that results from topical dosing of netarsudil ophthalmic solution 0.02% or netarsudil/latanoprost ophthalmic solution 0.02%/0.005%.

Reason for exclusion: Pregnant and breastfeeding women are routinely excluded from clinical trial populations when evaluating a new chemical entity.

Is it considered to be included as missing information? Yes

Rationale*:* Netarsudil is not absorbed systemically following topical ophthalmic administration, and maternal use is not expected to result in foetal exposure to the drug, nor exposure to a child during breastfeeding. However, it is considered prudent to capture use in this population as missing information.

Criterion: Hypersensitivity

Subjects with known hypersensitivity to any component of the formulation were excluded.

Reason for exclusion: Enrolling subjects with known hypersensitivity can place patients at risk and can affect compliance and assessment of safety.

Is it considered to be included as missing information?: No

Rationale: This group was excluded from the clinical trials for protection of human subjects and data integrity, it does not represent missing information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programme

Table SIV 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. However, 2 pregnancy cases were reported in the clinical trials
Breastfeeding women	1 subject, treatment duration 87 days with netarsudil 0.02% BID. Pregnancy outcome was healthy baby, delivered at 37 weeks. 1 subject, treatment duration 357 days with netarsudil 0.02% QD. Pregnancy outcome was miscarriage. The investigator considered the relationship between masked study drug(s) as not applicable.

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	These patients were not included in the clinical development program.
Children (<18 years)	Two subjects <18 years were enrolled. 1 subject, 14 years of age, with 360 days treatment duration with netarsudil 0.02% QD, completed the study with no AEs. 1 subject 11 years of age, in Timolol 0.5% BID for 371 days, completed the study with no AEs.
Geriatric Population (≥65 years)	547 subjects (netarsudil 0.02% QD) 294 subjects (netarsudil/latanoprost 0.02%/0.005%)
Population with relevant different ethnic origin	The clinical trials were conducted in the United States of America (USA) and Canada, and included patients of Native American, Asian, Black or African American, White and Other racial groups. Although no ethnic groups were excluded from clinical trials, most patients were white (73.0% to 90.9% across the phase II and III clinical trials with netarsudil and 64.7% to 84.9% across phase II and III clinical trials with netarsudil/latanoprost). There were no clinically relevant differences observed between the treatment groups across all studies in the assessment demographic characteristics.
Subpopulations carrying relevant genetic polymorphisms	This was not specifically investigated in the clinical development program. No genetic polymorphisms were excluded from the clinical trials.
Other	Not included in the clinical development program.

Part II: Module SV - Post-authorisation experience

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module: 17 June 2020

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Rhokiinsa

Netarsudil ophthalmic solution 0.02% was approved in the United States of America (USA) by the Food and Drug Administration (FDA) on 18 December 2017 for use in patients with OAG and OHT under the tradename Rhopressa®. Since product was launched in the USA on 30 April 2018 the cumulative patient exposure is estimated to be approximately 68,777 patient-years for Rhopressa by the DLP of this RMP.

Rhokiinsa was approved in Europe through the centralised procedure by the European Medicines Agency (EMA) in 2019 for use in patients with primary OAG and OHT. Product launch is pending and no post marketing exposure data are available at this time.

Roclanda

Netarsudil/Latanoprost 0.02%/0.005% ophthalmic solution was approved in the USA by the FDA on 13 March 2019 for use in patients with OAG and OHT under the tradename Rocklatan®. Since product was launched in the USA on 01 May 2019 the cumulative patient exposure is estimated to be approximately 15,326 patient-years for Rocklatan by the DLP of this RMP.

Part II: Module SVI - Additional EU requirements for the safety specification

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module: 17 June 2020

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

No evidence of drug abuse was reported in clinical trials using netarsudil ophthalmic solution nor any reports of withdrawal or rebound phenomena. Similarly, no evidence of drug abuse was reported in clinical trials using netarsudil/latanoprost ophthalmic solution nor any reports of withdrawal or rebound phenomena. Netarsudil does not belong to a category of therapeutic agents which are known to give rise to risk of dependency or addiction. There is no indication that netarsudil will be used recreationally, nor that it has the potential for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module: 11 Nov 2025

Part II: Module SVII - Identified and potential risks

Information in this section focuses on risks that may be associated with netarsudil as a new active substance, in line with guidance in Section V.C.1.1.4 of GVP Module V (Revision 2).

The safety concerns for latanoprost published by the CMDh have also been assessed according to the HaRP/ GVP V Rev.2 methodology. Considering that no ongoing additional risk minimisation measures, ongoing additional pharmacovigilance activities, nor essential targeted questionnaires are in place for any listed safety concern, no safety concern relating to latanoprost is included within this RMP for netarsudil products.

Netarsudil ophthalmic solution 0.02% and the fixed dose combination netarsudil/latanoprost 0.02%/0.005% ophthalmic solution represent a new class of ocular hypotensive agents with unique pharmacological mechanisms of action. Based on nonclinical and clinical studies, netarsudil ophthalmic solution 0.02% appears to reduce IOP by increasing trabecular outflow facility, decreasing production of aqueous humor, and reducing episcleral venous pressure.

Throughout the clinical development, the Applicant has evaluated the dose-response and dose frequency-response of this molecule, as well as its ocular and systemic safety (both as a single agent and in fixed combination with latanoprost).

The safety and efficacy of netarsudil ophthalmic solution for the reduction of elevated IOP in subjects with OAG or OHT was evaluated in 12 completed clinical studies across both netarsudil and netarsudil/latanoprost development programs which included a total of 1950 subjects were treated with netarsudil and 1515 subjects were treated with comparators. Within the netarsudil treatment groups, 1834 subjects were treated with netarsudil 0.02%. A total of 1545 subjects were treated with netarsudil 0.02% QD, the concentration approved as Rhokiinsa, and 289 subjects were treated with netarsudil 0.02% BID.

In the completed Phase III studies, treatment with netarsudil ophthalmic solution 0.02% QD demonstrated clinically relevant and statistically significant reductions in IOP from baseline which were non-inferior to timolol. Similar proportions of subjects in the netarsudil QD and timolol groups achieved a target IOP reduction of ≤17 mmHg. There were no clinically relevant differences in IOP reductions comparing the demographic subgroups (age, race, sex, and iris colour) in the netarsudil QD group. The optimal dosing regimen from an efficacy and safety perspective has been established to be 0.02% QD PM (in the evening).

The safety and efficacy of netarsudil/latanoprost ophthalmic solution for the reduction of elevated IOP in subjects with OAG or OHT was evaluated in 3 completed clinical studies which included a total of 628 subjects were treated with netarsudil/latanoprost and 1137 subjects were treated with comparators. Within the netarsudil/latanoprost treatment groups, 555 subjects were treated with netarsudil/latanoprost 0.02%/0.005%.

Topical ocular administration of netarsudil ophthalmic solution 0.02% QD in humans produced little or no quantifiable systemic exposure to the parent compound or its primary metabolite. This lack of systemic absorption is consistent with a lack of netarsudil-related systemic adverse events in the clinical studies, and it represents a safety benefit relative to other therapeutic classes of products commonly used to treat elevated IOP that have known systemic adverse effects.

Ocular AEs were the most commonly-reported AEs in the 12 completed clinical studies across both netarsudil and netarsudil/latanoprost development programs. A summary of the clinical safety data has been included in Section 2.7.4. For the risk analysis presented below, data presented in Section 2.7.4 was used and the following risks have been recognised as identified risks or potential risks with netarsudil. Unless otherwise stated, data presented was reported in clinical trials conducted as part of the netarsudil ophthalmic solution 0.02% development program.

Conjunctival hyperaemia (Identified, Not Important)

Conjunctival hyperaemia was the most frequently reported adverse event associated with netarsudil treatment in clinical trials and it is attributed to the vasodilation effect of the Rho kinase inhibitor drug class.

This event was reported in the majority of subjects (97%, 27/29) in the Phase I Studies where netarsudil 0.02% was administered QD in the morning.

In the Phase II studies, the most frequently reported ocular events in the netarsudil treatment groups included conjunctival hyperaemia and ocular hyperaemia. The reporting of these events was differentiated by the verbatim terms used to describe the event. If the lower level term (LLT) verbatim description was ocular hyperaemia, it was coded to the preferred term (PT) of ocular hyperaemia. All other verbatim terms related to "red eyes" were coded to conjunctival hyperaemia. In the Phase III studies, all verbatim terms indicating LLTs with PT of ocular hyperaemia were coded to a PT of conjunctival hyperaemia. As a result, the PT of ocular hyperaemia was not reported in the Phase 3 clinical trials.

In Phase II studies, conjunctival hyperaemia was reported as an AE in 45.0% of subjects (94/209). The incidences of conjunctival hyperaemia were dose-related following QD AM dosing in Study AR-13324-CS201 (0.01%: 50.0%; 0.02%: 57.1%; 0.04%: 73.7%). The QD AM dosing regimen resulted in a higher incidence of conjunctival hyperaemia compared to QD PM dosing in the subsequent Phase 2 study AR-13324-CS202 (0.01%: 38.7%; 0.02%: 38.9%). Almost all reports (98.9%: 93/94) of conjunctival hyperaemia in all netarsudil groups across the Phase II studies were considered treatment-related.

In Phase III studies, conjunctival hyperaemia was the most frequently reported ocular AE in the netarsudil treatment groups (0.02% QD 54.4% (456/839), 0.02% BID 69.9% (202/289)). Most of these events were regarded as treatment-related (93.2%, 613/658). The incidence of these AEs in netarsudil QD was lower in the shorter duration studies AR-13324-CS301 (conjunctival hyperaemia 53.2% (108/203), and AR-13324-CS304 (47.9% (168/351)) than in the longer duration studies AR-13324-CS302 60.6% (152/251), and AR-13324-CS303 (82.4% (28/34)), respectively. The incidence of conjunctival hyperaemia was higher for netarsudil BID in studies AR-13324-CS302 and AR-13324-CS303 (66.4% and 94.4% respectively).

The intensity and frequency of conjunctival hyperaemia was typically mild in severity. However, there was a relatively small proportion of subjects with moderate or severe hyperaemia who discontinued treatment because of this adverse event (0.02% QD 6.0% (50/839), 0.02% BID 27.0% (78/289)).

In the supportive Phase III studies PG324-CS301 and PG324-CS302 (evaluating the safety and efficacy of the netarsudil/latanoprost 0.02%/0.005% ophthalmic solution fixed dose combination product), the most common TEAE across all 3 treatment groups was conjunctival hyperaemia, reported in 42.6% of subjects (625/1468) in total (47.0%; 234/498 in the netarsudil group, 58.7%; 283/482 in the netarsudil/latanoprost group; and 22.1%;108/488 in the latanoprost group). When present, the majority of conjunctival hyperaemia cases were predominantly mild in severity.

An analysis of demographic subgroups demonstrated that conjunctival hyperaemia was reported in a higher proportion in white subjects when compared to other races QD: 61.3 vs. 34.1%; BID: 75.4 vs. 55.1%).

Cornea verticillata (Identified, Not Important)

The term "cornea verticillata" refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium (23,24). A variety of drugs that are both cationic and amphiphilic are known to induce cornea verticillata, which arise due to the lysosomal accumulation of phospholipids within corneal epithelial cells through a process called phospholipidosis.

Netarsudil is a cationic amphiphilic drug and the Applicant has shown that netarsudil can induce phospholipidosis in Chinese hamster ovary cells (AR-13324-IPH07), suggesting that the etiology of the netarsudil-induced corneal deposits is phospholipidosis. It is unusual for cornea verticillata to result in reduction of visual acuity or ocular symptoms and the deposits typically resolve with discontinuation of the drug (Mantyjarvi 1998).

Cornea verticillata was a common adverse event associated with netarsudil treatment and observed only in the Phase III studies. Corneal verticillata occurred in 20.9% of patients (0.02% QD 175/839). Cornea verticillata occurred at a higher incidence in the longer 6- and 12-month studies (AR-13324-CS302 QD 25.5%; BID 25.3%; AR-13324-CS303 QD 38.2%; BID 38.9%, and AR-13324-CS304 QD 24.5%) compared to the 3-month study (AR 13324-CS301 QD 5.9%).

In Study AR-13324-CS301, none of corneal deposits (cornea verticillata) AEs led to treatment discontinuation. In Study AR-13324-CS302, the incidence of mild verticillata in discontinued netarsudil QD subjects was similar to that in completing subjects: 17.0% (18/106) in discontinued subjects compared to 23.4% (34/145) in completing subjects. However, the incidence of moderate verticillata was slightly higher in discontinued subjects than in completing subjects. Cornea verticillata of moderate intensity was

associated with study drug discontinuation in 1.2% (3/251) and 5.5% (14/253) of netarsudil QD and BID subjects, respectively, and cornea verticillata of severe intensity was associated with study drug discontinuation in 0% (0/251) and 0.4% (1/253) of netarsudil QD and BID subjects, respectively. In Study AR-13324-CS303, 11.8% (4/34) and 16.7% (6/36) of subjects discontinued the study drug due to cornea verticillata in the netarsudil QD and BID groups. In study AR-13324-CS304, 4.0% (14/351) of subjects in the netarsudil QD treatment group discontinued study drug due to cornea verticillata.

This asymptomatic event, observed by the investigators only upon biomicroscopy, was generally graded as mild and similar to cornea verticillata associated with the approved anti-arrhythmic agent amiodarone.

The Applicant also conducted a Corneal Deposit Observation Study (AR-13324-OBS01) to further evaluate visual function in subjects who developed corneal deposits in the AR-13324-CS301 and -CS302 clinical studies. This long-term observational study demonstrated that cornea verticillata did not result in any apparent functional changes in vision. At the completion of the observational study, there was no clinically meaningful impact of cornea verticillata on visual function as measured by visual acuity, contrast sensitivity, and a visual function questionnaire. The AE resolved in all but 3 subjects (4 eyes); in these 3 subjects the AE had become reduced in severity and stabilized by the completion of the study (Section 2.3 of Section 2.7.4). After study completion, cornea verticillata resolved in 1 of these subjects and had improved in the other 2 subjects (3 out of 4 eyes).

Conjunctival haemorrhage (Identified, Not Important)

Conjunctival haemorrhage was the third most frequent adverse event in the clinical studies, which was typically reported as mild in severity and frequently considered treatment-related. In the Phase II studies, conjunctival haemorrhage was reported as a treatment-emergent adverse event in 13 subjects (AR-13324-CS202, 0.01% QD, 5.3% (4/75); 0.02% QD, 5.6% (4/72); PG324-CS201 0.02% QD, 6.4%, (5/78)). In the Phase III studies, conjunctival haemorrhage was also a common AE reported in the subjects who received netarsudil (17.6%, 199/1128). The incidence of conjunctival haemorrhage across the four Phase III studies was higher in the netarsudil group (QD: 15.8 to 20.6%; BID: 16.7 to 19.4%) compared to comparator drug used (0.8 to 3.1%). When present, conjunctival haemorrhage was typically reported as mild and was considered treatment-related (51.3% (102/199)).

In Study AR-13324-CS301, no subject was discontinued from the study due to the occurrence of conjunctival haemorrhage. In Study AR-13324-CS302, conjunctival haemorrhage of mild intensity was associated with study drug discontinuation in 2.8% (7/251) and 4.7% (12/253) of netarsudil QD and BID subjects, respectively, and conjunctival haemorrhage of moderate intensity was associated with study drug discontinuation in 0% (0/251) and 0.8% (2/253) of netarsudil QD and BID subjects. In Study AR-13324-CS303, 2.9% (1/34) and 0% (0/34) discontinued the study drug due to conjunctival haemorrhage in the QD and BID groups, respectively. In study AR-13324-CS304, one subject, 0.3% (1/351) discontinued study drug due to conjunctival haemorrhage of mild severity.

In the supportive Phase III study PG324-CS301, all conjunctival haemorrhage events were sporadic and graded as mild in severity except 1 moderate event in the netarsudil group, and the majority of these resolved with no sequalae morphology. Two subjects in the netarsudil group discontinued due to conjunctival haemorrhage. In the PG324-CS302 study, conjunctival haemorrhage was predominantly of mild severity and none of the events led to discontinuation. Almost all (45 out of 49 events) spontaneously resolved with no sequalae.

Blurred vision (Identified, Not Important)

Vision blurred was typically reported as mild and intermittent and considered to be treatment-related. In the Phase II studies, blurred vision was reported as a treatment-emergent AE in 12 subjects (AR-13324-CS201, 0.02% QD, 9.5% (2/21); 0.04% QD, 5.3 (1/19); AR-13324-CS202, 0.01% QD, 2.7% (2/75); 0.02% QD, 4.2 (3/72)). In the Phase III studies, it was reported as a treatment-emergent AE in 114 subjects (0.02% QD, 7.4% (62/839): 0.02% BID, 17.0% (49/289)) and it was considered related to netarsudil in 89 subjects (78.1% (89/114)).

Visual acuity reduced (Identified, Not Important)

Reduced visual acuity was typically reported as mild in severity. An evaluation of visual acuity results across all Phases I, II, and III studies demonstrated that mean changes from baseline in visual acuity were small, similar among all treatment groups and not clinically relevant. In the Phase III studies, visual acuity

reduced was reported as a treatment-emergent AE in 67 subjects (0.02% QD, 5.2% (44/839): 0.02% BID, 8.0% (23/289)) and in 46 (68.7%, (46/67) subjects it was reported as related to netarsudil.

Increased Lacrimation (Identified, Not Important)

Lacrimation increased was a less commonly reported TEAE when compared to other AEs mentioned above and it was moderate to severe in intensity when it led to discontinuation. In the Phase II studies, it was reported in 15 subjects (AR-13324-CS201, 0.02% QD, 4.8% (1/21); AR-13324-CS202, 0.01% QD, 5.3% (4/75); 0.02% QD, 6.9% (5/72)). In the Phase III studies, it was reported as a treatment emergent AE in 89 subjects (0.02% QD, 7.2% (60/839): 0.02% BID, 10.0% (29/289)) and in 74 subjects it was reported as related to netarsudil treatment (83.1% (74/89)).

Erythema of Eyelid (Identified, Not Important)

Erythema of Eyelid was reported at a low incidence and was rarely a reason for study drug discontinuation. In the Phase II studies, it was reported in 3 subjects (AR-13324-CS201, 0.02% QD, 4.8% (1/21); 0.04% QD, 5.3% (1/19), AR-13324-CS202, 0.01% QD, 1.3% (1/75)). In the Phase III studies, it was reported as a treatment emergent AE in 79 subjects (0.02% QD, 6.8% (57/839): 0.02% BID, 7.6% (22/289)) and in 72 subjects it was considered related to netarsudil treatment (91.1% (72/79)).

Eye irritation, symptoms of dry eyes, disruption of the tear film and corneal surface, due to use of eye drops containing preservatives (Potential, Not Important)

Patients with open-angle glaucoma and ocular hypertension are usually required to use eye drops for life. Presence of a preservative in an ocular medication has often been considered a culprit in damaging the epithelium (25). Therefore, a preservative in eye drops may increase the risk of both adverse effects on the ocular surface and the possibility of allergic reactions. The risk of damage increases with increased frequency of dosing due to increased exposure to preservatives.

Drug Hypersensitivity (Potential, Not Important)

In the pooled safety analysis in Phase III trials, drug hypersensitivity was reported as a non-ocular treatment related AE in a minority of subjects in the netarsudil treatment groups (0.02% QD: 2 subjects 0.02% BID: 1 subject). Skin reactions and other more serious allergic reactions might also occur in patients with known hypersensitivity to any ingredients in this product (Benzalkonium chloride, Mannitol, Boric acid, Sodium hydroxide) and it is contraindicated in these patients.

Eye and eyelid allergies have also been reported as treatment-related AEs in a minority of subjects using netarsudil.

Non-ocular AEs

The incidence of non-ocular treatment-related adverse events was low, most likely as a result of the limited systemic absorption of netarsudil. In the pooled safety analysis, non-ocular adverse events were mild in severity and not related, therefore no non-ocular AE has been identified as a risk except drug hypersensitivity as mentioned above.

SVII.1 Identification of safety concerns in the initial RMP submission

Table SVII 1 Safety concerns in the Initial RMP of Netarsudil 200 micrograms/ml Eye Drops, Solution, and Latanoprost + Netarsudil 50 micrograms/ml + 200 micrograms/ml Eye Drops, Solution

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Eye irritation, symptoms of dry eyes, disruption of the tear film and corneal surface, due to use of eye drops containing preservatives
Missing information	• Use in pregnancy and lactation • Long term safety of netarsudil (beyond 12 months) • Use in patients with compromised corneal epithelium

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

For the identified and potential risks, safety data are presented by the number and percentage of the adverse events seen in the clinical trials in the preceding section.

The identified risks of conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage are the most frequently reported ocular events in the netarsudil treatment groups, however these are evaluated as not important risks per the rationale provided below.

- Conjunctival hyperaemia is an expected pharmacological effect for the Rho kinase inhibitor drug class due to the vasodilation effect of the drug and it is not preventable. The majority of the conjunctival hyperaemia reports were mild in intensity and transient in nature. The incidences of conjunctival hyperaemia were both dose-related and higher following morning dosing.

- Cornea verticillata were asymptomatic and the finding of cornea verticillata due to netarsudil did not demonstrate any clinically meaningful impact on visual function. The incidence of cornea verticillata was not higher after 12 months of dosing in AR-13324-CS302 than it was after 6 months of dosing in AR-13324-CS304. This is evidence that the incidence is not likely to rise much beyond what was seen at 12 months in AR-13324-CS302. Since there are no significant risk factors identified there will be no preventative measures applicable for the risk of corneal verticillata.

- Conjunctival haemorrhage events were mostly mild in intensity and they were for the most part short-lived and self-resolving.

Other identified risks listed below were ocular adverse events occurring with less frequency and with minimal clinical impact on patients in relation to the severity of the indication treated. These are also not considered as important because they occurred in a small percentage of the patients, were of mild to moderate intensity and did not result in discontinuation of the study drug; in addition, they do not require any additional pharmacovigilance observation or activities or additional risk minimisation measures.

- Blurred vision

- Visual acuity reduced

- Increased lacrimation

- Erythema of eyelid

- Drug hypersensitivity

- Eye irritation, symptoms of dry eyes, disruption of the tear film and corneal surface, due to use of eye drops containing preservatives.

The following risk previously categorized as a safety concern under missing information is not considered important because it is a known risk that require no further characterisation and is followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers

- Use in patients with compromised corneal epithelium may result in corneal ADRs like reticular corneal epithelial oedema (RECE).

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Eye irritation, symptoms of dry eyes, disruption of the tear film and corneal surface, due to use of eye drops containing preservatives previously classified as important potential risk is to be removed from the list of safety concerns as outlined in the previous regulatory request in assessment report of Type IB variation, procedure No. EMA/VR/0000290523.

Use in pregnancy and lactation, Long term safety of netarsudil (beyond 12 months) and Use in patients with compromised corneal epithelium previously classified as missing information are to be removed from the list of safety concerns as outlined in the previous regulatory request in assessment report of Type IB variation, procedure No. EMA/VR/0000290523.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module | 11 Nov 2025

Part II: Module SVIII - Summary of the safety concerns

This RMP focuses on risks that may be associated with netarsudil as a new active substance, in line with guidance in Section V.C.1.1.4 of GVP Module V (Revision 2). As both Rhokiinsa and Roclanda contain the same concentration of netarsudil (0.02%) and are both administered as one drop to the affected eye(s) once daily in the evening, it is proposed both products share the same safety concerns as outlined below.

Table SVIII 1 Summary of safety concerns

Summary of the safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module: 11 Nov 2025

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance will involve adverse reactions reporting and signal detection as per the minimum set of activities contained in Directive 2001/83/EC and Regulation (EC) No 726/2004 and as described in the Pharmacovigilance System Master File. There are no additional routine pharmacovigilance activities planned.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module	17 June 2020

Part IV: Plans for post-authorisation efficacy studies

There are currently no planned or ongoing post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module	11 Nov 2025

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

This RMP focuses on risks that may be associated with netarsudil as a new active substance, in line with guidance in Section V.C.1.1.4 of GVP Module V (Revision 2). As both Rhokiinsa and Roclanda contain the same concentration of netarsudil (0.02%) and are both administered as one drop to the affected eye(s) once daily in the evening, it is proposed the risk minimisation plan outlined below is appropriate for both products.

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal products.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of risk management plan

Active substance(s) **(INN or common name)**	**Rhokiinsa®** Netarsudil mesylate (netarsudil) **Roclanda®** Latanoprost and Netarsudil mesylate (netarsudil)
MAH/MAA name	SANTEN Oy

Data lock point for this module	11 Nov 2025

SUMMARY OF RISK MANAGEMENT PLAN FOR RHOKIINSA (NETARSUDIL)

This is a summary of the risk management plan (RMP) for Rhokiinsa. The RMP details important risks of Rhokiinsa, how these risks can be minimised, and how more information will be obtained about Rhokiinsa's risks and uncertainties (missing information).

Rhokiinsa's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rhokiinsa should be used.

This summary of the RMP for Rhokiinsa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rhokiinsa's RMP.

I. The medicine and what it is used for

Rhokiinsa is authorised for the reduction of elevated intraocular pressure in adult patients with primary open-angle glaucoma or ocular hypertension (see SmPC for the full indication). It contains netarsudil as the active substance and it is given via eye drops.

Further information about the evaluation of Rhokiinsa’s benefits can be found in Rhokiinsa’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/rhokiinsa*

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Rhokiinsa together with measures to minimise such risks and the proposed studies for learning more about Rhokiinsa's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Rhokiinsa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rhokiinsa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

Not applicable.

SUMMARY OF RISK MANAGEMENT PLAN FOR ROCLANDA (LATANOPROST + NETARSUDIL)

This is a summary of the risk management plan (RMP) for Roclanda. The RMP details important risks of Roclanda, how these risks can be minimised, and how more information will be obtained about Roclanda's risks and uncertainties (missing information).

Roclanda's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Roclanda should be used.

This summary of the RMP for Roclanda should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Roclanda's RMP.

I. The medicine and what it is used for

Roclanda is authorised for the reduction of elevated intraocular pressure in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction (see SmPC for the full indication). It contains latanoprost and netarsudil as the active substances and it is given via eye drops.

Further information about the evaluation of Roclanda's benefits can be found in Roclanda's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/roclanda.*

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Roclanda together with measures to minimise such risks and the proposed studies for learning more about Roclanda's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Roclanda are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Roclanda. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Roclanda.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Roclanda.

Annex 4 - Specific adverse drug reaction follow-up forms

There are no specific adverse drug reaction follow-up forms.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

There are currently no proposed additional risk minimisation activities.