ROCKLATAN (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%

1. NAME OF THE MEDICINAL PRODUCT

Rocklatan 50 micrograms/ml + 200 micrograms/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 50 micrograms latanoprost and 200 micrograms netarsudil (as mesylate) .

Excipient(s) with known effect

Each ml of solution contains 200 micrograms benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless solution, pH 5 (approximately).

Osmolality: 280 mOsm/Kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocklatan is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.

4.2 Posology and method of administration

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

Posology

Use in adults, including the elderly
The recommended dosage is one drop in the affected eye(s) once daily in the evening. Patients should not instil more than one drop in the affected eye(s) each day.

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

Paediatric population
The safety and efficacy of Rocklatan in children below the age of 18 years have not been established. No data are available.

Method of administration

For ocular use.

Data on potential interactions specific to latanoprost + netarsudil are described in section 4.5. If latanoprost + netarsudil is to be used concomitantly with other topical ophthalmic medicinal products, each medicinal product should be administered at least five minutes apart. Due to netarsudil's vasodilating properties, other eye drops should be administered before latanoprost + netarsudil. Eye ointments should be administered last.

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

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Iris pigmentation

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia.

Increased iris pigmentation has not been shown to have any negative clinical sequelae and treatment with medicinal products containing latanoprost can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, treatment with medicinal products containing latanoprost may be discontinued.

Herpetic keratitis condition

Medicinal product(s) containing latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.

Macular oedema risk

Reports of macular oedema with medicinal products containing latanoprost have occurred mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Medicinal products containing latanoprost should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

Iritis/uveitis risk

In patients with known predisposing risk factors for iritis/uveitis, medicinal products containing latanoprost can be used with caution.

Asthma exacerbation

There is limited experience of latanoprost use in patients with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience with the combination.

Periorbital skin discolouration

Periorbital skin discolouration has been observed on treatment with medicinal products containing latanoprost, the majority of reports being in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with latanoprost.

Eyelash changes

Treatment with medicinal products containing latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

Benzalkonium chloride content

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

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

4.5 Interaction with other medicinal products and other forms of interaction

In vitro interaction studies have shown that precipitation can occur when eye drops containing thimerosal are mixed with latanoprost + netarsudil. Administer other eye drops at least five minutes apart (see section 4.2).

In vitro studies have indicated netarsudil has the potential to inhibit CYP450 isoenzymes in the cornea, however no clinical evidence of local pharmacokinetic interactions has been observed to date.

There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of latanoprost + netarsudil in pregnant women.

No effects during pregnancy are anticipated, since systemic exposure to netarsudil is negligible (see section 5.2). Animal studies with intravenous administration of netarsudil do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3).

Latanoprost has potentially harmful pharmacological effects during pregnancy and/or on the fetus/newborn child (see section 5.3).

Therefore, latanoprost + netarsudil should not be used during pregnancy.

Breast-feeding

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

Fertility

There are no data on the effects of netarsudil on male or female fertility. However, no effects are anticipated, since systemic exposure to netarsudil is negligible (see section 5.2). Latanoprost has not been found to have any effect on male or female fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Rocklatan has negligible influence on the ability to drive and use machines.
If transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common ocular adverse reaction observed is conjunctival hyperaemia which was reported in 46% of patients. Other ocular adverse reactions reported are instillation site pain (14%), cornea verticillata (12%) and eye pruritis (7%). The majority of adverse reactions reported in clinical studies using Rocklatan were ocular, mild to moderate in severity. Based on clinical studies, conjunctival hyperaemia which was reported in approximately 46% of patients led to discontinuation in 4.9% of patients.

Tabulated list of adverse reactions

The following adverse reactions have been reported with latanoprost + netarsudil, dosed once daily, and during clinical studies and post-marketing surveillance with the individual components latanoprost and netarsudil. Adverse reactions are presented according to the MedDRA system organ classification. Within each system organ class, the adverse reactions are classified by frequency according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000)

System Organ Classification	Frequency	Adverse reactions
Infections and infestations	Rare	herpetic keratitis[2]
Immune system disorders	Uncommon	hypersensitivity, vomiting
Nervous system disorders	Uncommon	headache, muscle contractions involuntary, dizziness, visual field defect[3]
Eye disorders	Very common	conjunctival hyperaemia[1], cornea verticillata[1], instillation site pain, iris hyperpigmentation[2], eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation and number of eyelashes)[2]

	Common	conjunctival haemorrhage, vision blurred, lacrimation increased, erythema of eyelid, eye pruritus, eye irritation, visual acuity reduced, eyelid oedema, punctate keratitis, corneal disorder, conjunctival oedema, conjunctivitis allergic, eye pain, dry eye, foreign body sensation in eyes, eyelid margin crusting, blepharitis, instillation site erythema, instillation site discomfort, vital dye staining cornea present
	Uncommon	eyelids pruritus, conjunctival disorder, corneal opacity, eye discharge, corneal deposits, conjunctivitis, dacryostenosis acquired, eye inflammation, eye paraesthesia, conjunctival follicles, eye swelling, meibomian gland dysfunction, corneal pigmentation, diplopia, noninfective conjunctivitis, abnormal sensation in eye, keratitis, refraction disorder, anterior chamber flare, conjunctival irritation, intraocular pressure increased, eyelid rash, eyelid skin dryness, growth of eyelashes, lacrimal disorder, iritis, visual impairment, corneal dystrophy, instillation site dryness, instillation site pruritus, instillation site reaction, eye complication associated with device, fatigue, instillation site paraesthesia, macular oedema including cystoid macular oedema[2], uveitis[2], ocular hyperaemia[3], diabetic retinopathy[3], eye allergy[3], ocular discomfort, eyelid disorder[3], ectropion[3], lenticular opacities[3], asthenopia[3], episcleral hyperaemia[3], halo vision[3], anterior chamber inflammation[3], blindness[3], conjunctivochalasis, eczema eyelids[3], glaucoma[3], iris adhesions[3], iris bombe[3], ocular hypertension[3], instillation site irritation[3], glassy eyes[3], instillation site oedema[3], conjunctival staining[3], optic nerve cup/disc ratio increased[3], madarosis[3], blepharal pigmentation, eye disorder, retinal haemorrhage, photophobia
	Rare	corneal oedema[2], corneal erosion[2], periorbital oedema[2], trichiasis[2], distichiasis[2], iris cyst[2], localised skin reaction on the eyelids[2], darkening of the palpebral skin of the eyelids[2], pseudopemphigoid of ocular conjunctiva[2]
	Very rare	periorbital and lid changes resulting in deepening of the eyelid sulcus[2]
Cardiac disorders	Uncommon	angina[2], palpitations[2]
	Very rare	angina unstable[2]
Respiratory, thoracic and mediastinal disorders	Uncommon	epistaxis, nasal congestion, nasal discomfort[3], rhinalgia[3] asthma[2], dyspnoea[2]
	Rare	asthma exacerbation[2]
Skin and subcutaneous tissue disorders	Common	dermatitis contact
	Uncommon	lichenification, dry skin, erythema, skin disorder, dermatitis allergic[3] petechiae, eczema
	Rare	pruritus[2]
Musculoskeletal and connective tissue disorders	Uncommon	pain in jaw, myalgia[2], arthralgia[2], polychondritis[3], muscular weakness, Sjogren's syndrome

General disorders and administration site conditions	Uncommon	chest pain[2]
Injury, poisoning and procedural complications	Uncommon	excoriation[3]

[1] See *Description of selected adverse reactions* for further information
[2] Additional adverse reaction observed with latanoprost monotherapy
[3] Additional adverse reaction observed with netarsudil monotherapy

Description of selected adverse reactions

Conjunctival hyperaemia
Conjunctival hyperaemia was the most frequently reported adverse reaction associated with latanoprost + netarsudil treatment in clinical studies and it is attributed to the vasodilation effect of the Rho kinase inhibitor medicinal product class. Conjunctival hyperaemia was typically mild in severity and sporadic. However, there was a relatively small proportion of subjects with moderate or severe hyperaemia who discontinued treatment because of this adverse reaction (5.0% in Phase 3 clinical studies).

Cornea verticillata
Cornea verticillata occurred in approximately 13% of the patients in controlled Phase 3 clinical studies. The cornea verticillata seen in latanoprost + netarsudil-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. The majority of cornea verticillata resolved upon discontinuation of treatment. The incidence of cornea verticillata was higher in certain subpopulations: elderly (≥65 years) versus non-elderly (18.8 vs. 11.5%); males versus females (18.8 vs. 13.0%) and in white versus other races (21.7 vs. 2.5%).

Iris pigmentation
Rocklatan contains latanoprost which is a prostaglandin F2 α analogue. The majority of adverse reactions associated with latanoprost are ocular in nature. In a 5-year latanoprost safety study, 33% of patients developed iris pigmentation (section 4.4).

This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown. In studies with latanoprost, the onset of the change is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable for five years. The effect of increased pigmentation beyond five years has not been evaluated. The iris colour change is slight in the majority of cases and often not observed clinically. The incidence in patients with mixed colour irides ranged from 7 to 85%, with yellow-brown irides having the highest incidence. In patients with homogeneously blue eyes, no change has been observed and in patients with homogeneously grey, green or brown eyes, the change has only rarely been seen.

The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical studies to date.

Neither naevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical studies.

Other special populations

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

4.9 Overdose
Systemic exposure to the netarsudil component of latanoprost + netarsudil following topical ocular administration has been shown to be negligible.

Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if latanoprost is overdosed.

If latanoprost is accidentally ingested the following information may be useful: one bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system.

Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost.

If topical overdose of latanoprost + netarsudil should occur, the eye(s) may be flushed with tap water. Treatment of an overdose would include supportive and symptomatic therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiglaucoma preparations and miotics, ATC code: S01EE51

Mechanism of action

Rocklatan contains two active substances: latanoprost and netarsudil. These two components lower IOP by increasing the outflow of aqueous humor. Although both latanoprost and netarsudil lower IOP by increasing aqueous humor outflow, their mechanisms of action are different.

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

Studies in animal and man indicate that the main mechanism of action for latanoprost, a prostaglandin F2α analoque, is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

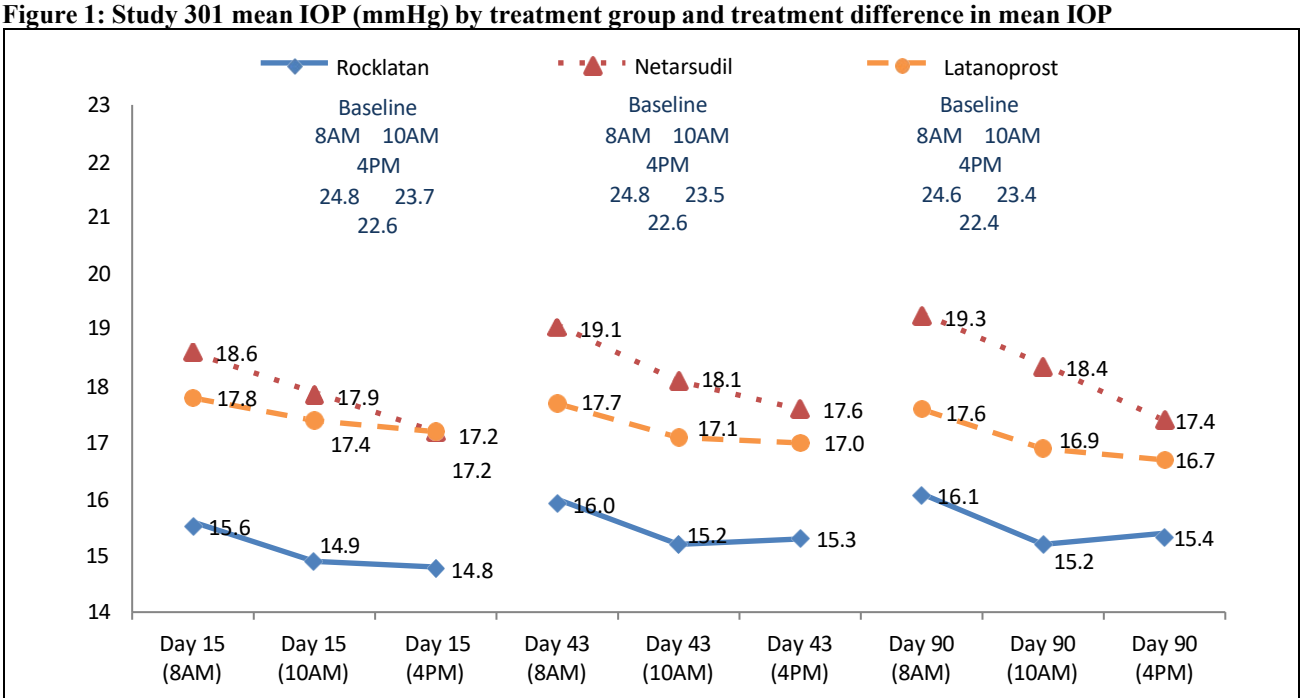
Clinical efficacy and safety

Rocklatan was evaluated in 3 randomized, double-blind, multicentre Phase 3 clinical studies in 1,686 patients with open-angle glaucoma and ocular hypertension. Studies 301 and 302 enrolled

subjects with IOP <36 mmHg and compared IOP lowering effect of latanoprost + netarsudil dosed once daily to individually administered netarsudil 0.02% once daily and latanoprost 0.005% once daily. The treatment duration was 12 months for Study 301 and 3 months for Study 302. The median age of study participants was 66 years (range 18 to 99 years). Study 303 assessed the ocular hypotensive efficacy of latanoprost + netarsudil relative to Ganfort® (bimatoprost 0.03%/timolol 0.5%). The treatment duration was 6 months.

Studies 301 and 302 were designed to show superiority of latanoprost + netarsudil when dosed once daily in the evening over its individual components netarsudil 0.02% once daily and latanoprost 0.005% once daily. The primary efficacy outcome measure was least squares (LS) mean IOP at each of 9 timepoints measured at 08:00, 10:00 and 16:00 on day 15, day 43 and day 90. The average IOP lowering effect of latanoprost + netarsudil was 1 to 3 mmHg greater than monotherapy with either netarsudil 0.02% or latanoprost 0.005% throughout 3 months (Figures 1 and 2). In Study 301 IOP reductions were maintained, showing statistical superiority of latanoprost + netarsudil throughout the 12-month treatment period. In all cases, the differences in the LS mean IOP were clinically relevant and statistically significant ($p < 0.0001$) through month 3. Approximately 30% of subjects included in the Phase 3 studies had a baseline IOP of ≥27 mmHg (132, 136 and 143 in the latanoprost + netarsudil, latanoprost and netarsudil treatment groups, respectively). In these subjects, latanoprost + netarsudil showed statistically significantly superior IOP-lowering efficacy to each of its components at all time points. Across both studies, compared to latanoprost alone, the combination product reduced IOP by a further 1.7 mmHg to 3.7 mmHg, and compared to netarsudil alone by a further 3.4 mmHg to 5.9 mmHg.

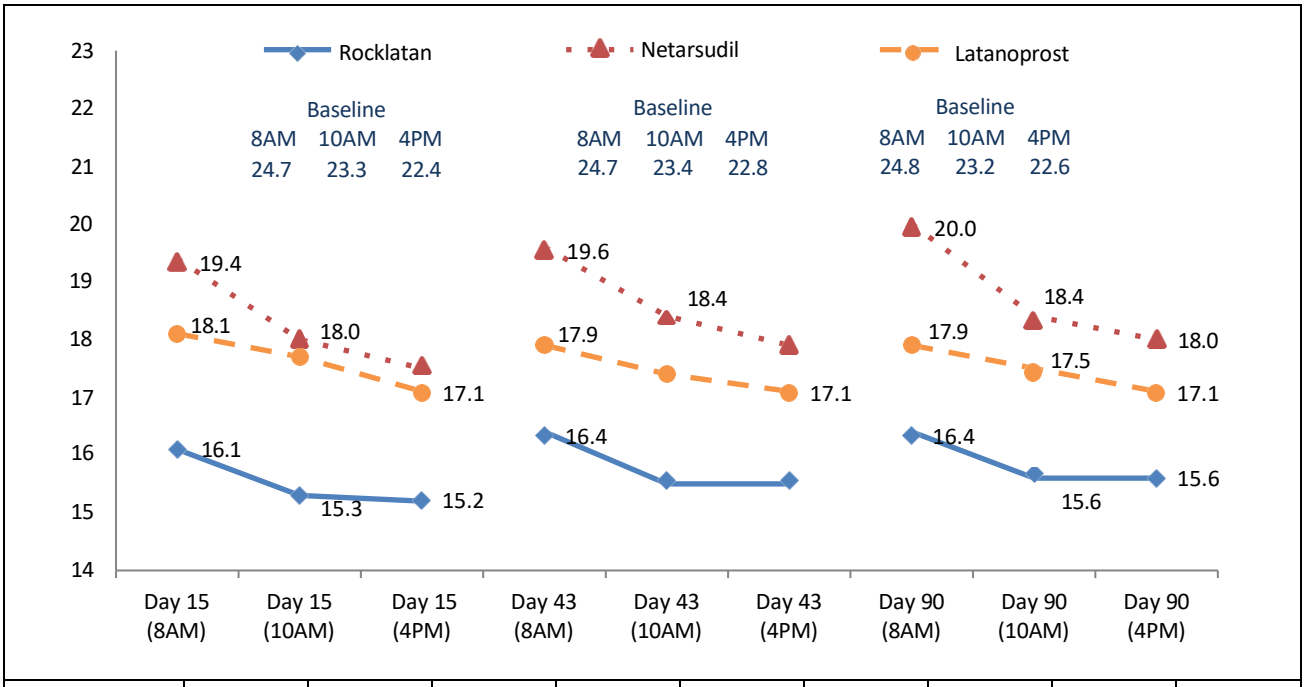
Figure 1: Study 301 mean IOP (mmHg) by treatment group and treatment difference in mean IOP



latanoprost + netarsudil vs. netarsudil 95% CI	**3.0 (2.5, 3.6)**	**3.0 (2.4, 3.6)**	**2.4 (1.9, 3.0)**	**3.2 (2.6, 3.8)**	**2.9 (2.3, 3.5)**	**2.3 (1.7, 2.8)**	**3.1 (2.5, 3.8)**	**3.2 (2.5, 3.8)**	**2.0 (1.4, 2.6)**
latanoprost + netarsudil vs. latanoprost 95% CI	**2.3 (1.7, 2.8)**	**2.6 (2.0, 3.2)**	**2.3 (1.8, 2.9)**	**1.7 (1.1, 2.4)**	**1.9 (1.3, 2.5)**	**1.7 (1.1, 2.2)**	**1.5 (0.9, 2.1)**	**1.7 (1.1, 2.3)**	**1.3 (0.7, 1.9)**

The LS mean IOP at each post-baseline time point was derived using an analysis of covariance adjusted for baseline IOP and based on observed data for all randomized subjects (238 in latanoprost + netarsudil group, 244 in netarsudil group, 236 in latanoprost group).

Figure 2: Study 302 mean IOP (mmHg) by treatment group and treatment difference in mean IOP



latanoprost + netarsudil vs. netarsudil 95% CI	**3.4 (2.8, 3.9)**	**2.7 (2.2, 3.2)**	**2.2 (1.7, 2.8)**	**3.2 (2.6, 3.8)**	**2.9 (2.3, 3.4)**	**2.3 (1.8, 2.9)**	**3.6 (3.0, 4.2)**	**2.8 (2.3, 3.4)**	**2.4 (1.9, 2.9)**
latanoprost + netarsudil vs. latanoprost 95% CI	**2.0 (1.5, 2.6)**	**2.4 (1.9, 2.9)**	**1.9 (1.3, 2.4)**	**1.5 (0.9, 2.1)**	**1.9 (1.3, 2.4)**	**1.6 (1.0, 2.1)**	**1.5 (0.9, 2.2)**	**2.0 (1.4, 2.5)**	**1.5 (1.0, 2.1)**

The LS mean IOP at each post-baseline time point was derived using an analysis of covariance adjusted for baseline IOP and based on observed data for all randomized subjects (245 in latanoprost + netarsudil group, 255 in netarsudil group, 250 in latanoprost group).

Approximately 67% of subjects included in the latanoprost + netarsudil treatment groups of Phase 3 studies were caucasian and 30% black or african american. Over half were aged ≥ 65 years. With the exception of the incidence of cornea verticillata (section 4.8); no other difference in safety profile was observed between races or age groups.

Completion rates in studies 301 and 302 were lower in the latanoprost + netarsudil treatment groups when compared with the latanoprost group. Discontinuation rates due to adverse events at month 3 were 8.7% for the pooled latanoprost + netarsudil treatment group versus 7.6% for the pooled netarsudil group and 1.0% for the pooled latanoprost group. Discontinuation rates due to adverse events at month 12 in Study 301 were 19.7% for the latanoprost + netarsudil treatment group versus 21.7% for the netarsudil group and 1.7% for the latanoprost group. The majority of discontinuations were associated with ocular events. The most frequently reported adverse event associated with discontinuation in the latanoprost + netarsudil group was conjunctival hyperemia (7.6% at month 12). The majority of ocular adverse events reported with netarsudil + latanoprost were mild in intensity.

Study 303 was a prospective, double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month study assessing the safety and ocular hypotensive efficacy of latanoprost + netarsudil compared to bimatoprost + timolol in 430 subjects with elevated intraocular pressure. Subjects were randomly assigned to a planned fixed-dose treatment regimen with latanoprost + netarsudil one drop (218 subjects), once daily (QD) each evening in both eyes (OU) or comparator bimatoprost + timolol (212 subjects) one drop QD each evening OU for approximately 180 days following a washout period.

The primary efficacy outcome was the comparison of latanoprost + netarsudil to bimatoprost + timolol for Mean IOP at specified timepoints at Week 2, Week 6, and Month 3. The primary analysis was

performed on the ITT population with imputation by Markov Chain Monte Carlo (MCMC) method. This analysis demonstrated clinical non-inferiority of latanoprost + netarsudil ophthalmic solution relative to bimatoprost + timolol dosed QD in the ITT population with the upper limit of the 95% CIs around the difference (latanoprost + netarsudil - bimatoprost + timolol) ≤ 1.5 mmHg at all 9 time points and ≤ 1.0 mmHg at the majority (6 out of 9) of time points from Week 2 through Month 3, meeting the criteria for success. The threshold for clinical non-inferiority of latanoprost + netarsudil QD relative to bimatoprost + timolol QD (the between-group difference ≤ 1.5 mmHg) was demonstrated in the PP population at 8 out of 9 time points (08:00, 10.00, and 16:00) at week 2, through month 3 using the MCMC method. However, clinical non inferiority was not met overall since at the week 6 08:00 time point, the upper bound 95% CI was 1.55. Overall, there was a similar mean IOP reduction throughout the day of approximately 9.5 mmHg between both the latanoprost + netarsudil and bimatoprost + timolol treatment group.
The overall rate of discontinuation from the study treatment due to a TEAE was 11.2%. More subjects in the latanoprost + netarsudil QD treatment group discontinued from the study treatment due to a TEAE (20.2%) compared to the bimatoprost + timolol QD group (1.9%), and the majority of TEAEs leading to discontinuation were ocular TEAEs. No serious treatment-related adverse events were reported in any treatment group, and the safety profile remains consistent with the known profile for latanoprost + netarsudil, and/or latanoprost or netarsudil alone.

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

5.2 Pharmacokinetic properties

Absorption

The systemic exposures of netarsudil and its active metabolite, AR-13503, were evaluated in 18 healthy subjects after topical ocular administration of netarsudil 200 micrograms/ml once daily (one drop bilaterally in the morning) for 8 days. There were no quantifiable plasma concentrations of netarsudil (lower limit of quantitation (LLOQ) 0.100 ng/ml) post dose on Day 1 and Day 8. Only one plasma concentration at 0.11 ng/ml for the active metabolite was observed for one subject on Day 8 at 8 hours post-dose.

Latanoprost (molecular weight 432.58) is an isopropyl ester prodrug which per se is inactive, but after hydrolysis to the acid of latanoprost becomes biologically active. The prodrug is well absorbed through the cornea and all active substance that enters the aqueous humour is hydrolysed during the passage through the cornea. Studies in man indicate that the peak concentration in the aqueous humour is reached about two hours after topical administration. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eyelids. Only minute quantities of latanoprost reach the posterior segment.

Biotransformation

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

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The half-life in plasma is 17 minutes in man. The main metabolites, the 1,2-dinor and

1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

5.3 Preclinical safety data

Netarsudil

Non-clinical data with netarsudil reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to development. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures. In pregnant rats, 0.1 mg/kg/day showed no adverse maternal or embryofoetal effects, whereas increased post-implantation loss and reduced foetal viability was observed at 0.3 mg/kg/day and higher. In pregnant rabbits, 3 mg/kg/day showed no maternal or embryofoetal effects, whereas an increase in post-implantation loss and a decrease in foetal weight were observed at 5 mg/kg/day.

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

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

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

Latanoprost

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Generally, latanoprost is well tolerated with a safety margin between clinical ocular dose and systemic toxicity of at least 1000 times. High doses of latanoprost, approximately 100 times the clinical dose/kg body weight, administered intravenously to unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In animal studies, latanoprost has not been found to have sensitising properties.

In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.

In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lymphoma and mouse micronucleus test. Chromosome aberrations were observed *in vitro* with human lymphocytes. Similar effects were observed with prostaglandin F2α, a naturally occurring prostaglandin, and indicates that this is a class effect.

Additional mutagenicity studies on *in vitro*/*in vivo* unscheduled DNA synthesis in rats were negative and indicate that latanoprost does not have mutagenic potency. Carcinogenicity studies in mice and rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats, no embryotoxicity was observed at intravenous doses (5, 50 and 250 micrograms/kg/day) of latanoprost. However, latanoprost induced embryolethal effects in rabbits at doses of 5 micrograms/kg/day and above.

The dose of 5 micrograms/kg/day (approximately 100 times the clinical dose) caused significant embryofoetal toxicity characterised by increased incidence of late resorption and abortion and by reduced foetal weight.

No teratogenic potential has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
Opened bottle: 4 weeks after first opening the bottle. Do not store above 30 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Store in the original carton in order to protect from light.

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

6.5 Nature and contents of container

Rocklatan is supplied in polypropylene (PP) bottles (2.5 ml fill in a 5ml container), with PP dropper tips and high-density polyethylene (HDPE) caps, and anti-tamper seals.

Carton containing 1 or 3 bottles. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Santen Pharmaceutical Co., Ltd. Shiga Plant
348-3, Aza-Suwa, Oaza-Shide, Taga-cho, Inukami-gun, Shiga, Japan

8. PRODUCT REGISTRATION HOLDER

SANTEN PHARMA MALAYSIA SDN. BHD.
Unit #23A-10, Q Sentral,
No.2A, Jalan Stesen Sentral 2, Kuala Lumpur Sentral,
50470 Kuala Lumpur, Malaysia.

9. DATE OF REVISION OF THE TEXT

Aug 2026