ROCKLATAN OPHTHALMIC SOLUTION, 0.02% W/V / 0.005% W/V

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

ROCKLATAN (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a fixed dose combination of a Rho kinase inhibitor and a prostaglandin $F_{2\alpha}$ analogue indicated for the reduction of elevated intraocular pressure (IOP) in patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin F2α analogue or Rho kinase inhibitor provides insufficient IOP reduction.

2. DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose in the evening. The dosage of ROCKLATAN should not exceed once daily.

ROCKLATAN may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

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

3. DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing netarsudil 0.2 mg/mL and latanoprost 0.05 mg/mL.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance(s) or to any of the excipients.

5. WARNINGS AND PRECAUTIONS

5.1 Pigmentation

ROCKLATAN contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. Beyond 5 years the effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with ROCKLATAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

5.2 Eyelash Changes

ROCKLATAN contains latanoprost which may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

ROCKLATAN contains latanoprost which should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular

inflammation because it may exacerbate inflammation.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. ROCKLATAN should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular edema (such as diabetic retinopathy and retinal vein occlusion).

5.5 Herpetic Keratitis

Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost. ROCKLATAN should be used with caution in patients with a history of herpetic keratitis. ROCKLATAN should be avoided in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues and in cases of active herpes simplex keratitis because it may exacerbate inflammation.

5.6 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.7 Use with Contact Lenses

Contact lenses should be removed prior to the administration of ROCKLATAN and may be reinserted 15 minutes after administration.

5.8 Benzalkonium chloride content

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

5.9 Asthma exacerbation

There is limited experience with 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.

5.10 Long term use

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

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The most common ocular adverse reaction observed in controlled clinical studies with ROCKLATAN was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual

acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

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 nonelderly (18.8 vs. 11.5%); males versus females (18.8 vs. 13.0%) and in white versus other races (21.7 vs. 2.5%).

Other adverse reactions that have been reported with the individual components and not listed above include:

- Netarsudil 0.02%

Instillation site erythema, corneal staining, increased lacrimation, and erythema of eyelid.

- Latanoprost 0.005%

Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reactions.

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[3], vomiting
Nervous system disorders	Uncommon	headache, muscle contractions involuntary, dizziness[2,3], 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, photophobia, 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

System Organ Classification	Frequency	Adverse reactions
		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[3], eyelid disorder[3], ectropion[3], lenticular opacities[3], asthenopia[3], episcleral hyperemia[3], halo vision[3], anterior chamber inflammation[3], blindness[3], conjunctivochalasis[3], 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], retinal haemorrhage
	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[3]
	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 *ADVERSE REACTIONS, Clinical Trials Experience* for further information
[2] Additional adverse reaction observed with latanoprost monotherapy
[3] Additional adverse reaction observed with netarsudil monotherapy

7. DRUG INTERACTIONS

In vitro drug interaction studies have shown that precipitation can occur when eye drops containing thimerosal are mixed with ROCKLATAN. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

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.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ROCKLATAN ophthalmic solution or its pharmacologically active ingredients (netarsudil and latanoprost) in pregnant women to inform any drug associated risk. However, systemic exposure to netarsudil from ocular administration is low *[see Clinical Pharmacology]*.

Reproduction studies of latanoprost showed embryofetal lethality in rabbits. No embryofetal lethality was observed at a dose approximately 15 times higher than the recommended human ophthalmic dose (RHOD). Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures. ROCKLATAN should not be used during pregnancy.

Data

Animal Data

Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the RHOD, based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

Reproduction studies have been performed with latanoprost in rats and rabbits. In 4 of 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD.

8.2 Lactation

Risk Summary

There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ROCKLATAN and any potential adverse effects on the breast-fed child from ROCKLATAN.

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.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use

With the exception of cornea verticillata *[see section 6]*, no difference in the safety profile for latanoprost + netarsudil Conjunctival hyperaemia has been observed between subjects aged <65 or ≥65 years.

8.5 Compromised corneal epithelium or co-existing ocular pathologies

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

8.6 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.

8.7 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.

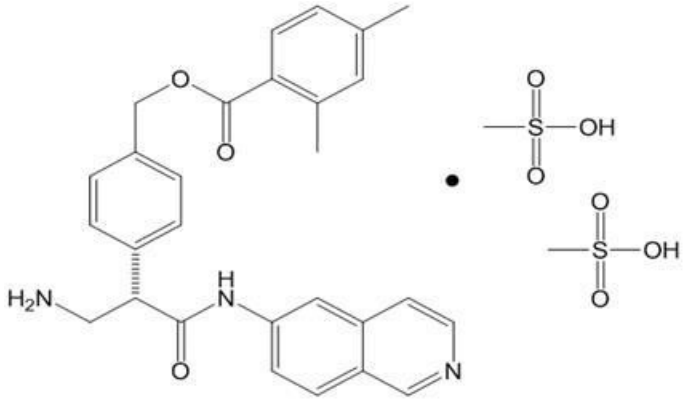
Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost.

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.

9. DESCRIPTION

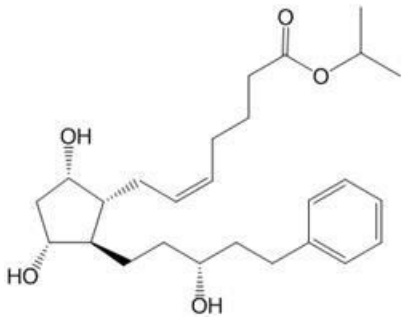
ROCKLATAN (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a fixed dose combination of a Rho kinase inhibitor and a prostaglandin $F_{2\alpha}$ analogue.

The chemical name of netarsudil mesylate is: (*S*)-4-(3-amino-1-(isoquinolin-6-yl-amino)-1-oxopropan- 2-yl)benzyl 2,4-dimethylbenzoate dimesylate. Its molecular formula is $C_{30}H_{35}N_3O_9S_2$ and its chemical structure is:



Netarsudil mesylate is a light yellow to white powder that is freely soluble in water, soluble in methanol, sparingly soluble in dimethyl formamide, and practically insoluble in dichloromethane and heptane.

The chemical name of latanoprost is: isopropyl-(*Z*)-7[(1*R*,2*R*,3*R*,5*S*) 3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:



Latanoprost is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol. It is practically insoluble in water.

ROCKLATAN (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is supplied as a clear, sterile aqueous opthalmic solution of netarsudil mesylate and latanoprost with pH 4.2-5.3 and osmolality 250-340 mOsm/kg. Each mL of ROCKLATAN contains 0.2 mg of netarsudil (equivalent to 0.28 mg of netarsudil mesylate) and 0.05 mg latanoprost. Benzalkonium chloride, 0.02%, is added as a preservative. The inactive ingredients are: boric acid, mannitol, sodium hydroxide to adjust pH, and water for injection.

10. CLINICAL PHARMACOLOGY

10.1 ATC code: S01EE51 Mechanism of Action

ROCKLATAN is comprised of two components: netarsudil and latanoprost. Each of these two components decreases elevated IOP. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and glaucomatous visual field loss.

ROCKLATAN is believed to reduce IOP by increasing the outflow of aqueous humor.

10.2 Pharmacokinetics

Absorption

The systemic exposures of netarsudil and its active metabolite, AR-13503, were evaluated in 18 healthy subjects after topical ocular administration of netarsudil ophthalmic solution 0.02% once daily (1 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 1 plasma concentration at 0.11 ng/mL for the active metabolite was observed for 1 subject on Day 8 at 8 hours post-dose.

Distribution

The distribution volume in humans is 0.16 ± 0.02 L/kg. Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration.

Metabolism

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

Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion

The elimination of the acid of latanoprost from human plasma is rapid ($t_{½}$ = 17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose are recovered in the urine after topical and intravenous dosing, respectively.

11. NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the RHOD) for up to 20 and 24 months, respectively.

Mutagenesis

Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test.

Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed *in vitro* with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative.

Impairment of Fertility

Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Latanoprost has not been found to have effects on male or female fertility in animal studies.

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.

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 sensitizing properties.

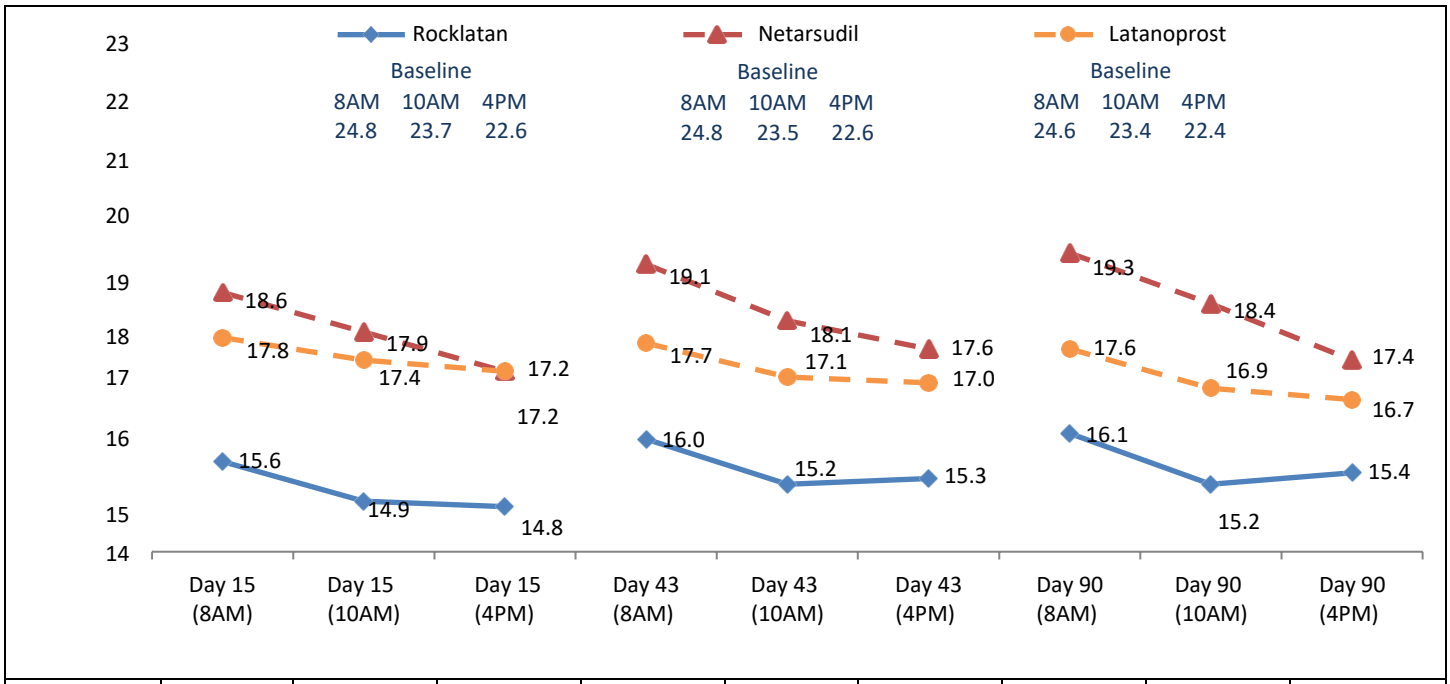
In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation 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.

12. CLINICAL STUDIES
ROCKLATAN was evaluated in 2 randomized, double-blind, multicentre Phase 3 clinical studies in 1,468 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).

The studies 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.

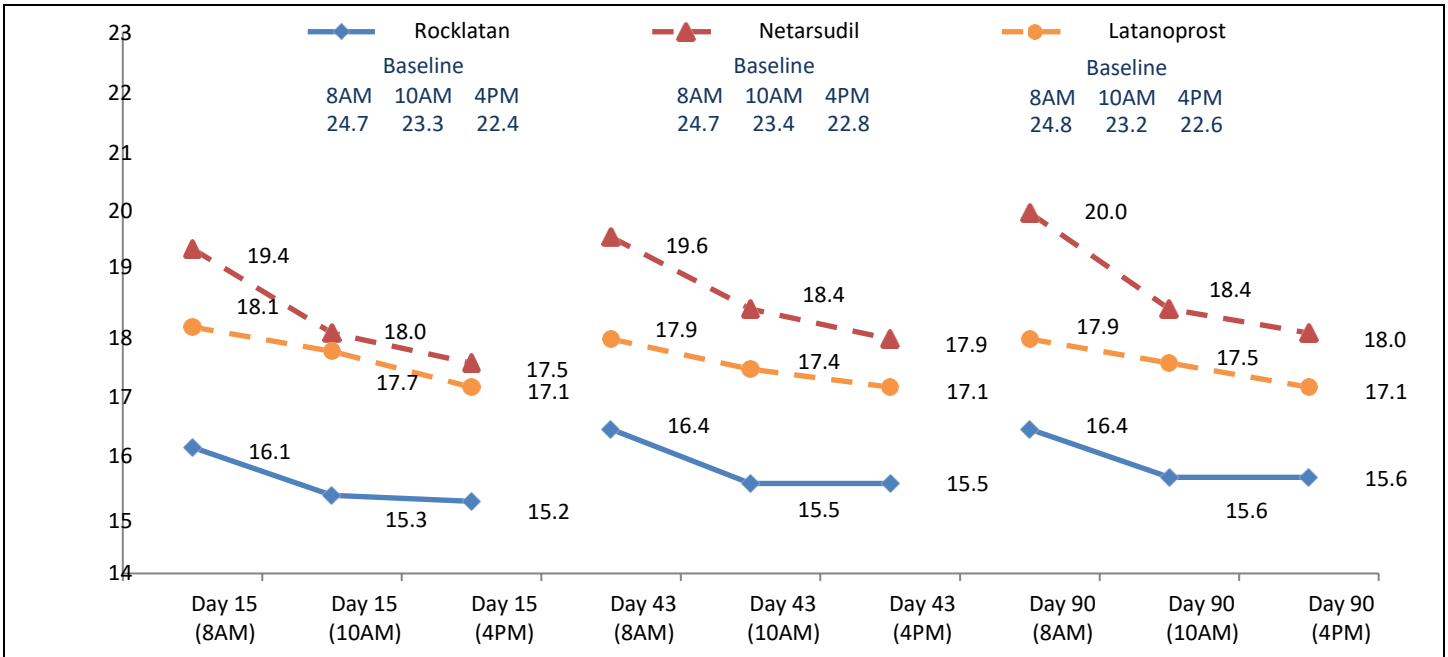
Figure 1: Study 301 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP



Rocklatan 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)**
Rocklatan 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 least square 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 Rocklatan 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



Rocklatan 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)**
Rocklatan 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 least square 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 Rocklatan 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 6.1); no other difference in safety profile was observed between races or age groups.

Completion rates in Phase 3 studies 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 hypaeremia (7.6% at month 12). The majority of ocular adverse events reported with netarsudil + latanoprost were mild in intensity.

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.

13. HOW SUPPLIED/STORAGE AND HANDLING

ROCKLATAN (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is supplied sterile in clear low density polyethylene bottles with opaque white polyethylene dropper tips and white polypropylene screw caps.

2.5 mL fill in a 4 mL container

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

14. PATIENT COUNSELING INFORMATION

Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of ROCKLATAN *[see Warnings and Precautions]*.

Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with ROCKLATAN. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

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

When to Seek Physician Advice

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

Use with Contact Lenses

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

Use with Other Ophthalmic Drugs

If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes between applications.

Missed Dose

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

15. Manufactured by

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