PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROCLANDA 50 µg/ml + 200 µg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 50 µg latanoprost and 200 µg netarsudil (as mesylate).

Excipient(s) with known effect:

ROCLANDA contains 0,02 % *w/v* benzalkonium chloride as preservative.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless solution, practically free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with ROCLANDA should only be initiated by an ophthalmologist or a health care 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

Children should not use ROCLANDA. The safety and efficacy of ROCLANDA in paediatric patients, below the age of 18 years, have not been established.

Method of administration

ROCLANDA is for ocular use.

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 contact with the eye, surrounding structures, fingers or any other surface to avoid contamination of the eye drops solution. Serious damage to the eye, and subsequent loss of vision, may result from using contaminated solutions.

Contact lenses should be removed prior to instillation of ROCLANDA and can be reinserted 15 minutes following instillation (see section 4.4).

If ROCLANDA is to be used concurrently with other topical ophthalmic medicines, each medicine should be administered at least five minutes apart. Due to the vasodilating properties of the netarsudil component of ROCLANDA, other eye drops should be administered prior to ROCLANDA instillation. Eye ointments should be administered last. Refer to section 4.5 for information on possible medicine interactions.

4.3 Contraindications

- Hypersensitivity to the active substance(s), benzalkonium chloride, or to any of the excipients listed in section 6.1.
- Pregnancy and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Iris pigmentation

The latanoprost component of ROCLANDA may gradually change the eye colour by increasing the amount of brown pigment in the iris (see section 4.8). Prior to treatment initiation, 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. Intraocular pressure (IOP) reduction is reportedly similar in patients regardless of the development of increased iris pigmentation and therefore, treatment with latanoprost-containing medicines can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, treatment with latanoprost, as

contained in ROCLANDA, may be discontinued (section 4.8).

Herpetic keratitis
Medicines containing latanoprost, as contained in ROCLANDA, should be used with caution in patients with a history of herpetic keratitis. Furthermore, it 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
Macular oedema, including cystoid macular oedema, has been reported with latanoprost use, as contained in ROCLANDA; 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). ROCLANDA should be used with caution in such patients.

Iritis/uveitis risk
In patients with known predisposing risk factors for iritis/uveitis, medicines containing latanoprost, like ROCLANDA, can be used with caution.

Asthma exacerbation
There is limited experience of latanoprost use, as contained in ROCLANDA, in patients with asthma; however, cases of asthma, exacerbation of asthma, acute asthma attack, coughing and dyspnoea have been reported. Asthmatic patients should therefore be treated with caution.

Periorbital skin discolouration
Periorbital skin discolouration, including eyelid skin darkening, has been reported with latanoprost, as contained in ROCLANDA. Experience to date report that periorbital skin discolouration is not permanent and, in some cases, has reversed while continuing with latanoprost treatment.

Eyelash changes
Treatment with latanoprost, as contained in ROCLANDA, 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, or misdirected growth of eyelashes. Eyelash changes are reversible upon treatment discontinuation.

Benzalkonium chloride
ROCLANDA contains 0,02 % *w/v* benzalkonium chloride as a preservative.
Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes, and may affect the tear film and corneal surface. It should be used with caution in dry-eye patients and in patients where the cornea may be compromised. Patients should be monitored in cases of prolonged use.
Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Contact lenses should be removed prior to instillation of ROCLANDA and can be reinserted 15 minutes following instillation (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction
There have been reports of paradoxical elevations in IOP following the concurrent ophthalmic administration of two prostaglandin analogues. Therefore, the use of ROCLANDA with another medicine containing a prostaglandin analogue, a prostaglandin or prostaglandin derivatives, is not recommended.

Precipitation can occur when eye drops containing thiomersal are mixed with latanoprost and netarsudil, as contained in ROCLANDA. If ROCLANDA is to be used concurrently with other topical ophthalmic medicines, each medicine should be administered at least five minutes apart (see section 4.2). Due to the vasodilating properties of the netarsudil component of ROCLANDA, other eye drops should be administered prior to ROCLANDA instillation. Eye ointments should be administered last.

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

Based on the low systemic bioavailability of netarsudil following topical administration (undetectable), and on the low systemic bioavailability of latanoprost, systemic medicine interactions with topical ophthalmic application of ROCLANDA is unlikely. With respect to the potential for interaction between ROCLANDA and other concomitantly administered topical ophthalmic medicines, none have been reported in any of the clinical studies with netarsudil/latanoprost, as contained in ROCLANDA. Netarsudil/latanoprost, as contained in ROCLANDA, has been administered safely in conjunction with other ophthalmic medicines and diagnostic medicines, including antibiotics, anaesthetics, cycloplegics, mydriatics, ocular lubricants and vital dyes.

4.6 Fertility, pregnancy and lactation

Pregnancy

ROCLANDA is contraindicated in pregnancy (see section 4.3).

There is no or limited amount of data from the use of ROCLANDA in pregnant women; however, the latanoprost component of ROCLANDA has potentially harmful pharmacological effects during pregnancy and/or on the foetus/newborn child (see section 5.3), and therefore, should not be used during pregnancy.

In terms of the netarsudil component of ROCLANDA, 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).

Breastfeeding

ROCLANDA is contraindicated during breastfeeding (see section 4.3).

The latanoprost component of ROCLANDA and its metabolites may pass into human milk, and safety in breastfeeding has not been established.

It is unknown whether the netarsudil component of ROCLANDA (or its metabolites), are excreted in human milk. While no effects on the breastfed newborn/infant are anticipated, since the systemic exposure of breastfeeding women to netarsudil is expected to be negligible, no relevant clinical data are available.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from ROCLANDA treatment, taking into consideration the benefit of breastfeeding for the child, and the benefit of ROCLANDA treatment for the woman.

Fertility

There is no data on the effects of the netarsudil component of ROCLANDA 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

ROCLANDA has negligible influence on the ability to drive and use machines. However, transient blurred vision can occur during instillation; until this has resolved, patients should not drive or use machines.

4.8 Undesirable effects

a) Summary of the safety profile

Conjunctival hyperaemia is the most common ocular adverse reaction reported, reported in 46 % of patients, and led to treatment discontinuation in 4,9 % 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 during clinical studies with ROCLANDA were ocular, which were mild to moderate in severity.

b) Tabulated list of adverse reactions

The following adverse reactions have been reported with the latanoprost and netarsudil ophthalmic combination, 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 (≥ 1/1000 to <1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000).

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Rare	Herpetic keratitis[2]
Immune system disorders	Uncommon	Hypersensitivity
Nervous system disorders	Uncommon	Headache, involuntary muscle contractions, 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, blurred vision, increased lacrimation, erythema of eyelid, eye pruritus, eye irritation, reduced visual acuity, eyelid oedema, punctate keratitis, corneal disorder,

		conjunctival oedema, allergic conjunctivitis, 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, acquired dacryostenosis, 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, increased intraocular pressure, 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 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	Unstable angina[2]
Respiratory, thoracic and mediastinal disorders	Uncommon	Epistaxis, nasal congestion, nasal discomfort[3], rhinalgia[3], asthma[2], dyspnoea[2]
	Rare	Asthma exacerbation[2]
Gastrointestinal disorders	Uncommon	Vomiting, nausea[2]
Skin and subcutaneous tissue disorders	Common	Contact dermatitis, rash[2]
	Uncommon	Lichenification, dry skin, erythema, skin disorder, allergic dermatitis[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 section c) Description of selected adverse reactions for further information.
[2] Additional adverse reaction observed with latanoprost monotherapy.
[3] Additional adverse reaction observed with netarsudil monotherapy.

c) Description of selected adverse reactions

Conjunctival hyperaemia

Conjunctival hyperaemia, typically mild in severity, and sporadic, was the most frequently reported adverse reaction associated with the latanoprost and netarsudil ophthalmic combination, as contained in ROCLANDA, during clinical studies. There was however, a relatively small proportion of subjects with moderate or severe hyperaemia, who discontinued treatment due to conjunctival hyperaemia. It is attributed to the vasodilation effect of the netarsudil component of ROCLANDA and is also a known adverse effect associated with latanoprost.

Cornea verticillata

Cornea verticillata occurred in approximately 13 % of the patients treated with either ROCLANDA or netarsudil monotherapy during controlled Phase 3 clinical studies. It did not result in any apparent visual functional changes in patients, and the majority of cornea verticillata resolved upon treatment discontinuation. Cornea verticillata was reported only in the ROCLANDA and netarsudil groups, and it generally occurred at a higher rate in patients ≥ 65 years of age, in males and in Caucasian patients.

Iris pigmentation

ROCLANDA contains latanoprost which is a prostaglandin F2α analogue. The majority of adverse reactions associated with latanoprost are ocular in nature. In a 5-year latanoprost safety study, it is reported that 33 % of patients developed iris pigmentation (section 4.4).
The eye colour change is due to increased melanin content in the stromal melanocytes of the iris (rather than due to an increase in number of melanocytes). In most cases, the brown pigmentation around the pupil spreads concentrically towards the periphery of the affected iris, but the entire iris, or parts of it, may become more brownish. The change in iris colour is mild in the majority of cases and may not be detected clinically. It has not been associated with any symptom or pathological changes in clinical studies to date.
This change in eye colour has predominantly been seen in patients with mixed coloured irides that contain the colour brown at baseline, i.e., blue-brown, grey-brown, yellow-brown and green-brown, with the highest incidence reported in patients with yellow-brown irides. In patients with homogeneously blue eyes, no change has been reported, and in patients with homogeneously grey, green or brown eyes, the change has been reported infrequently.

Onset of increased iris pigmentation reportedly occurs within the first year of treatment (usually within the first 8 months), less frequently during the second or third year, and has not been reported after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable by five years. The effects of increased pigmentation beyond five years have not been evaluated, and the increase in brown iris pigment has reportedly not been shown to progress further upon treatment discontinuation; the resultant colour change, however, may be permanent.
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 reported.

Other special populations

Elderly

With the exception of cornea verticillata (see above), no difference in the safety profile for latanoprost and netarsudil, as contained in ROCLANDA, has been observed in patients aged < 65 or ≥ 65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Systemic exposure to the netarsudil component of ROCLANDA following topical ocular administration has been shown to be negligible (see section 5.2).
Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if latanoprost, as contained in ROCLANDA, is overdosed.
If ROCLANDA is accidentally ingested, the following information regarding the latanoprost component may be useful: one bottle contains 125 µg latanoprost. More than 90 % is metabolised during the first pass through the liver. It is reported that intravenous infusion of 3 µg/kg in healthy volunteers induced no symptoms; however, a dose of 5,5 – 10 µg/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 µg/kg without major effects on the cardiovascular system.
Intravenous administration of latanoprost in monkeys has reportedly 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 ROCLANDA 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

Pharmacological classification: A 15.4 Ophthalmic preparations: Others.
Pharmacotherapeutic group: Ophthalmologicals, antiglaucoma preparations and miotics.
ATC code: S01EE51

Mechanism of action

ROCLANDA contains two active substances: latanoprost and netarsudil. These two components lower IOP by increasing the outflow of aqueous humour. Although both latanoprost and netarsudil lower IOP by increasing aqueous humour 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 report that the main mechanism of action for latanoprost, a prostaglandin F2α analogue, is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

Clinical efficacy and safety

ROCLANDA was evaluated in 3 randomised, double-blind, multicentre, Phase 3 clinical studies, in 1686 patients with open-angle glaucoma and ocular hypertension. Studies 301 and 302 enrolled subjects with IOP < 36 mmHg and compared the IOP-lowering effect of ROCLANDA, dosed once daily, to individually-administered 0,02 % netarsudil once daily, and 0,005 % latanoprost once daily. The treatment duration was 12 months for Study 301 and 3 months for Study 302.
Studies 301 and 302 were designed to show superiority of ROCLANDA when dosed once daily, in the evening, over its individual components, 0,02 % netarsudil once daily and 0,005 % latanoprost 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 ROCLANDA was 1 to 3 mmHg greater than monotherapy with either 0,02 % netarsudil or 0,005 % latanoprost throughout 3 months. In Study 301 IOP reductions were maintained, showing statistical superiority of ROCLANDA 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. In these subjects, ROCLANDA showed statistically significantly superior IOP-lowering efficacy to each of its components at all time points. Across both studies, compared to latanoprost alone, ROCLANDA 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.

Given that every millimetre of reduction in IOP can be significant in delaying disease progression and reducing the risk of glaucomatous vision loss, it is clinically meaningful that netarsudil/latanoprost provides reductions in IOP that are on average approximately 2,0 mmHg greater than either of its individual components.

Approximately 67 % of subjects included in the ROCLANDA 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 (see section 4.8); no other difference in safety profile was observed between races or age groups, and analyses of demographic subgroups showed no statistically significant effect of the demographic characteristic on the ocular hypotensive superiority of ROCLANDA; it was equally as effective in males and females, in older subjects ≥ 65 years and younger subjects < 65 years, and across all ethnic groups.

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

5.2 Pharmacokinetic properties

Absorption

Netarsudil mesylate has shown minimal or negligible absorption into the systemic circulation, following ocular dosing both in nonclinical toxicology studies, and in a Phase 1 clinical study, in healthy subjects. 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 % (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. The peak concentration in the aqueous humour is reportedly 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 metabolised 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 embryofoetal 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. It is reported that latanoprost is generally 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 µg/eye/day in rabbits or monkeys (clinical dose is approximately 1,5 µg/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 µg/eye/day has also been reported 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 µg/kg/day), of latanoprost. However, it is reported that latanoprost induced embryo-lethal effects in rabbits, at doses of 5 µg/kg/day and above.

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

No teratogenic potential has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Boric acid

Mannitol
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Precipitation can occur when eye drops containing thiomersal are mixed with latanoprost and netarsudil, as contained in ROCLANDA. If ROCLANDA is to be used concurrently with other topical ophthalmic medicines, each medicine should be administered at least five minutes apart (see section 4.2).

6.3 Shelf life

3 years.
Opened bottle: 4 weeks after first opening the bottle, stored at or below 25 °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 medicine, see section 6.3.

6.5 Nature and contents of container

ROCLANDA is supplied in clear, low-density polyethylene bottles (2,5 ml fill in a 4 ml container), with opaque-white, low-density polyethylene tips, opaque-white, polypropylene screw caps, and anti-tamper seals, packed in cartons containing 1 or 3 bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER

59/15.4/0831

DATE OF APPROVAL: 30 JUNE 2026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 June 2026

10. DATE OF REVISION OF THE TEXT

30 June 2026