℞ For the use only of a Registered Medical Practitioner or a Hospital or Laboratory.

Ripasudil Eye Drops 0.4% w/v

STERILE

RipaRock™ रिपारॉक

EYE DROPS

Centaur

1.0 GENERIC NAME

Ripasudil Eye Drops 0.4% w/v

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Ripasudil Hydrochloride Hydrate equivalent to Ripasudil ..... 4 mg

Benzalkonium Chloride IP..... 0.1 mg

(As preservative)

3.0 DOSAGE FORM AND STRENGTH

Eye Drops; 4 mg/ml

4.0 CLINICAL PARTICULARS

4.1. Therapeutic indication

To treat glaucoma and ocular hypertension when other medicines for glaucoma have insufficient effect or cannot be used.

4.2. Posology and method of administration

Posology

Use in adults including the elderly

Instill one drop into the affected eye(s) twice daily.

Use in paediatric population

Safety in low birth weight infants, newborns, infants, and children has not been established.

Method of Administration: For ocular use only.

When dispensing the drug: Instruct patients on the following:

1) In the instillation, the patient should tilt the head backwards, open the affected eye, instill the drug into the conjunctival sac, close the eyelid for 1 to 5 minutes while compressing the lacrimal part, and open the eye.
2) Be careful during the instillation to avoid direct contact of the tip of the container with the eye in order to prevent contamination of the drug.
3) Instill with an interval of at least 5 minutes when using the drug in combination with other ophthalmic solutions.

4.3 Contraindications

Ripasudil must not be used in the condition:

- Hypersensitivity to the active ingredient or to any of the excipients of the medicine.

4.4. Special warnings and precautions for use

Acute primary angle-closure glaucoma

Consider treatments other than drug therapy, such as surgical therapy, when using Ripasudil Eye Drops for acute primary angle-closure glaucoma.

Conjunctival hyperaemia

In clinical studies conducted prior to the time of approval in Japan, conjunctival hyperaemia in association with the use of Ripasudil has been reported. The event usually occurs transiently at the time of instillation, but be cautious if it continues. Take any appropriate measures such as discontinuation of treatment if this event occurs.

Conjunctivitis (including conjunctivitis allergic) and blepharitis (including allergic blepharitis)

In clinical studies conducted prior to the time of approval in Japan, conjunctivitis (including conjunctivitis allergic) and blepharitis (including allergic blepharitis) have been reported in association with the use of Ripasudil. The incidence of conjunctivitis allergic and blepharitis allergic tends to be high in patients with long-term instillation. Take any appropriate measures such as discontinuation of treatment if these events occur.

Contact lenses

Ripasudil Eye Drops has not been studied in patients wearing contact lenses. The preservative in Ripasudil Eye Drops, benzalkonium chloride may be adsorbed by the soft contact lens. Patients must be instructed to remove contact lenses prior to the application of Ripasudil Eye Drops and wait at least 15 minutes after instillation of the dose before reinsertion.

Use in paediatric population

Safety in low birth weight infants, newborns, infants, and children has not been established (there is no use experience).

4.5 Drug Interactions

No interaction studies have been performed.

4.6 Fertility, pregnancy, and lactation

Pregnancy

The safety of Ripasudil Eye Drops has not been established in pregnant women. Ripasudil Eye Drops should be used in pregnant women or possibly pregnant women only when therapeutic benefits are deemed to outweigh potential risks.

Breastfeeding

Animal studies (rats, oral administration) have shown that the drug was extracted in breast milk. Do not instill Ripasudil Eye Drops in breastfeeding women. If use of Ripasudil Eye Drops is unavoidable, breastfeeding should be suspended.

Fertility

No current data.

4.7 Effects on ability to drive and use machines

No findings suggesting that Ripasudil Eye Drops affects the ability to drive or operate machinery or impairment of mental ability were obtained.

4.8 Undesirable Reaction

Summary of the safety profile

In clinical studies conducted by the time of approval in Japan, 500 out of 662 subjects (75.5%) experienced adverse reactions. The main adverse reactions included conjunctival hyperaemia in 457 subjects (69.0%), conjunctivitis (including conjunctivitis allergic) in 71 subjects (10.7%), and blepharitis (including allergic blepharitis) in 68 subjects (10.3%).

Summary of adverse reactions

Adverse reactions and frequencies observed in clinical studies conducted by the time of approval in Japan are listed below by body site or by mechanism of onset of events.

	≥ 5%	≥ 0.1% and < 5%
Eye	Conjunctival hyperaemia, conjunctivitis (including conjunctivitis allergic), blepharitis (including allergic blepharitis), eye irritation	Corneal epithelial disorder (such as corneal erosion and punctate keratitis), eye pruritus, abnormal sensation in eye, eye discharge, eye pain, conjunctival follicles, intraocular pressure increased
Hypersensitivity		Rash, erythema

Corneal thickness tended to decrease in clinical studies. Decreases in corneal thickness caused by instillation of Ripasudil Eye Drops were reversible.

Postmarketing experience

Following adverse reactions have been reported, but the incidence of events cannot be calculated and are unknown because these events include the events reported as spontaneous reports.

Hypersensitivity	Incidence unknown
Eye	Eyelid oedema, vision blurred
Hypersensitivity	Contact dermatitis

Reporting of side effects or suspected adverse reaction: If you experience any side effects, talk to your doctor or pharmacist or report to indiadrugsafety@akums.in. You can also report side effects directly via the National Pharmacovigilance Program of India by calling on 18003133363. By reporting side effects, you can help provide more information on the safety of this product.

4.9 Overdose

No overdoses were observed during the development phase of Ripasudil Eye Drops. A topical overdose is not likely to occur or to be associated with toxicity. If overdose with Ripasudil Eye Drops occurs, treatment should be symptomatic and supportive.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics

Mechanism of Action

Inhibition of Rho kinase to facilitate aqueous outflow from the conventional outflow pathway via the trabecular meshwork and Schlemm's canal has been suggested as the IOP-lowering mechanism of action by ripasudil.

(1) Ripasudil selectively inhibited human ROCK-1 and ROCK-2, which are isoforms of Rho kinases (in vitro).
(2) After a single instillation of Ripasudil Eye Drops to rabbits, the aqueous outflow rate was significantly increased compared to the group treated with the vehicle.

(3) A single instillation of Ripasudil Eye Drops to rabbits did not affect the volume of uveoscleral outflow or aqueous production.

Pharmacodynamic Effects

After a single instillation of Ripasudil hydrochloride hydrate ophthalmic solution at 0.0625% to 0.5% to rabbits and the same solution at 0.1% to 0.4% to monkeys, a concentration-dependent IOP-lowering effect was observed.

5.2 Pharmacokinetic properties

Plasma Concentration and Urinary Excretion

Ripasudil Eye Drops was instilled repeatedly to healthy Japanese male adults at 1 drop/eye dose in both eyes twice daily for 7 days, and the changes of Ripasudil and its main metabolite M1 (isoquinoline ring position 1 hydroxylated form) over time in plasma concentrations and their pharmacokinetic parameters are shown in Figure 1 and Table 1. The entry of Ripasudil into the systemic circulation and the elimination thereof from the body were rapid. In addition, most of Ripasudil and M1 were excreted in the urine by 12 hours after completion of repeated instillation.

Figure-1. Changes Over Time in Plasma Concentration After Repeated Instillation in Healthy Male Adults

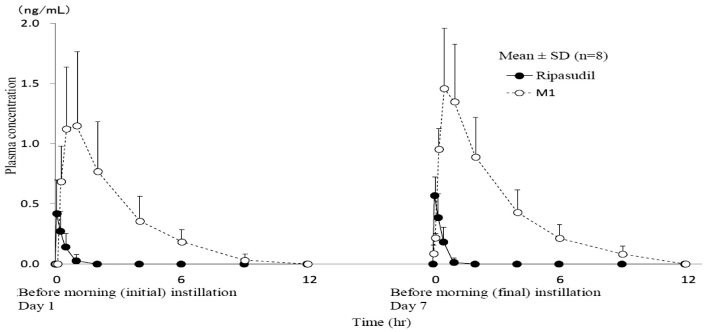


Table-1. Plasma Pharmacokinetic Parameters After Repeated Instillation in Healthy Male Adults

		t_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}\tau}$ (ng/mL)	$t_{1/2}$ (hr)
Ripasudil	Day 1	0.083 [0.0] n=7	0.420±0.278 n=8	0.183±0.135 n=8	–
	Day 7	0.083 [56.6] n=8	0.622±0.161 n=8	0.231±0.091 n=8	0.455 n=1
M1	Day 1	0.500 [37.6] n=8	1.198±0.582 n=8	3.838±2.085 n=8	–
	Day 7	0.500 [31.4] n=8	1.465±0.504 n=8	4.761±1.869 n=8	2.189±0.465 n=8

Mean ± SD, except t_{max}, for which the median (coefficient of variation (%)) is shown.

Entry into the Ocular Tissues

After a single dose of Ripasudil Eye Drops 50 μL) was instilled to both eyes of pigmented rabbits, the drug in the cornea and the aqueous humor reached the maximum concentration (68135.4 ng/g and 4126.39 ng/mL, respectively) by 0.25 hour and then was rapidly eliminated. In the lens, the drug reached the maximum concentration (154.37 ng/g) by 0.5 hour and then was slowly eliminated. After a single dose of 14C-ripasudil hydrochloride ophthalmic solution 1.0% (50 μL) was instilled to pigmented rabbits, the drug rapidly entered each ocular tissue. In the ocular tissues, a high radioactivity concentration was detected particularly in the iris/ciliary body and the retina/choroid, which are tissues containing melanin. After instillation twice daily for 7 days, the radioactivity concentration in the tissues containing melanin was obviously higher than after the single-dose instillation, and the radioactivity concentration tended to disappear gradually in all tissues.

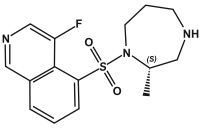
6.0 NON CLINICAL PROPERTIES

In the 2.0% (twice daily) group in the 13-week repeated instillation study in rabbits and the 4.0% (4 times daily) group in the 13-week repeated instillation study in dogs, irreversible degeneration of lens fibers with opacification was observed in the suture line of the anterior lens. Such changes in the lens are thought to have been caused by the inhibition of formation of actin stress fibers by the Rho kinase inhibiting effect of Ripasudil Eye Drops, which led to the inhibition of differentiation into the fiber cells of the lens and subsequent extension and migration.

7.0 DESCRIPTION

Ripasudil, as hydrochloride hydrate (K-115), is a specifc Rho-associated coiled-coil containing protein kinase (ROCK) inhibitor used for the treatment of glaucoma and ocular hypertension. It was first approved for treatment in Japan in September 2014. This medication is available in the form of a 0.4% eye drop solution under the brand name Glanatec. Ripasudil is a well-tolerated medication that is used when other drugs have been proven to be non-effective or cannot be administered.

Molecular formula is $C_{15}H_{21}ClFN_3O_3S$ and a molecular weight is 395.9 g/mol. The structural formula of Ripasudil is: -



- HCl
- 2 H_2O

8.0 PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities: Not applicable

8.2. Shelf life: As on carton

8.3. Packaging information: RipaRock Eye Drops is available in 3ml and 5 ml vial.

8.4. Storage and handling instruction: Store below 25°C. Protect from light & moisture. Do not freeze. KEEP OUT OF REACH OF CHILDREN.

9.1 Adverse reactions: Refer part 4.8

9.2 Drug Interactions: Refer part 4.5

9.3 Dosage: Refer part 4.2

9.4 Storage: Refer part 8.4

9.5 Risk factors: Refer part 4.4

9.6 Self-monitoring information: NA

9.7 Information on when to contact a health care provider or seek emergency help:

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing Physician.

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 Ripasudil Eye Drops.

Use with Contact Lenses: Advise patients that Ripasudil Eye Drops contains benzalkonium chloride, which may be absorbed by soft contact lenses.

Contact lenses should be removed prior to instillation of Ripasudil Eye Drops and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs: Advise patients that if more than one 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.

9.8 Contraindications: Refer part 4.3

10. Manufactured by: Pure & Cure Healthcare Pvt. Ltd.

11. Licence Number with date: 51/UA/SC/P-2013 on dated 27/01/2022

12. Date of revision: 22/11/2023

DATE OF PREPARATION: June – 2022

Marketed by:
CENTAUR PHARMACEUTICALS PVT. LTD.
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Santacruz (E), Mumbai - 400 055.

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