SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ryjunea 0.1 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml eye drops contains 0.1 mg of atropine sulfate.

One drop (about 0.03 ml) contains approximately 3 mcg of atropine sulfate.

Excipient with known effect

1 ml of Ryjunea 0.1 mg/ml solution contains 0.1 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution (eye drops)

The solution is a clear and colourless liquid with a pH of 5.4 and an osmolality of 280 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ryjunea is indicated for slowing the progression of myopia in paediatric patients. Treatment may be initiated in children aged 3-14 years with a progression rate of 0.5 D or more per year and a severity of -0.5 D to -6.0 D.

4.2 Posology and method of administration

Ryjunea should only be initiated by an ophthalmologist or a healthcare professional who has myopia within their scope of practice.

Posology

The recommended dose of Ryjunea 0.1 mg/ml is one drop into each eye once daily. Administration at bedtime is recommended.

Treatment should be assessed during regular clinical evaluation. Consider tapering and stopping treatment once myopia is stabilised (less than 0.5 D progression over 2 years) during adolescence. Continue monitoring for one year after cessation of treatment. Consider restarting treatment in case of subsequent myopia progression (0.5 D or worse per year, see section 4.4).

Missed dose
If one dose is missed, treatment should continue with the next dose as normal.

Paediatric population
The safety and efficacy of Ryjunea in children aged less than 3 years has not been established. No data are available.

Method of administration

Ocular use.

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

Contact lenses should be removed before instillation of the eye drops and may be reinserted after fifteen minutes (see section 4.4).

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least fifteen minutes apart. Eye ointments should be used last.

To maintain sterility, contact of the container with the eye or eyelids should be avoided.

4.3 Contraindications

Hypersensitivity to atropine sulfate or to any of the excipients listed in section 6.1.

Known hypersensitivity to other anticholinergics like ipratropium and tiotropium.

Patients with primary glaucoma or angle-closure glaucoma.

4.4 Special warnings and precautions for use

Photophobia and accommodative dysfunction

After using atropine sulfate, accommodative dysfunction and increased sensitivity to bright light can be expected due to mydriasis. The effect could last up to 14 days. Photochromatic lenses may be used as needed to reduce discomfort due to photophobia.

Rebound myopia progression upon discontinuation

Discontinuation of atropine sulfate eye drops may lead to rebound myopia progression. Continue monitoring for one year after cessation of treatment. Consider restarting treatment in case of rebound myopia progression (0.5 D or worse per year, see section 4.2).

Synechiae

Atropine sulfate may increase the risk of adherence of the iris and lens.

Cataract

Depending on the type and opacity of the cataract, visual acuity and refraction may not be accurately assessed.

Amblyopia and strabismus

Atropine sulfate can cause blurred vision which may exacerbate these conditions.

Progressive syndromic myopia of childhood

Before starting treatment with atropine, it is important to rule out progressive syndromic myopia of childhood, such as glaucoma, retinitis pigmentosa, congenital hemeralopia, and myelinated nerve fiber syndrome. These conditions do not evolve the same way as typical progressive myopia and should not be treated with atropine.

Patients with cardiac disorders

Atropine sulfate must be used and dosed with special caution in patients with tachycardia, heart failure, coronary stenosis and hypertension. Patients who have suffered a recent heart attack may experience tachycardic arrhythmias up to ventricular fibrillation while being administered atropine sulfate.

Risk of hyperthermia

As the capability for temperature regulation may be affected by inhibition of sweating, atropine sulfate must be used with caution in high ambient temperature and in patients with fever due to the risk of hyperthermia.

Spastic paralysis

An increased susceptibility to atropine has been reported in children with spastic paralysis; therefore Atropine sulfate must be used with special caution in these patients.

Down's syndrome

An increased susceptibility to atropine has been reported in children with Down's syndrome; therefore, atropine sulfate must be used with special caution in these patients.

Excipients

This medicinal product contains 0.1 mg benzalkonium chloride in each ml. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. This medicinal product should be used with caution in dry eye patients and in patients where the cornea may be compromised. Such patients should be monitored in case of prolonged use.

Contact lenses should be removed prior to administration and may be reinserted 15 minutes after administration. Benzalkonium chloride is known to be absorbed by soft contact lenses and may change the colour of contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Sympathomimetics

The possibility for systemic drug-drug interactions is considered low with atropine sulfate eye drops but it should be used with precaution when used in combination sympathomimetics like dobutamine, dopamine, norepinephrine, epinephrine or isoproterenol because mydriasis may be enhanced (see section 4.4).

Anticholinergics

If significant systemic absorption of ophthalmic atropine sulfate occurs, concurrent use of other anticholinergics or medicinal products with anticholinergic activity like antihistamines, phenothiazines, tricyclic and tetracyclic antidepressants, amantadine, quinidine, disopyramide and metoclopramide may result in potentiated anticholinergic effects.

Carbachol, physostigmine or pilocarpine

Concurrent use with atropine sulfate may interfere with the antiglaucoma action of carbachol, physostigmine or pilocarpine (see also section 4.3). Also, concurrent use may counteract the mydriatic effect of atropine sulfate.

Antimyasthenic medicinal products like pyridostigmine and neostigmine, potassium citrate, potassium supplements

If significant systemic absorption of ophthalmic atropine sulfate occurs, concurrent use may increase the chance of toxicity and/or side effects like constipation, nausea and vomiting because of the anticholinergic induced slowing of gastrointestinal motility.

CNS depression-producing medical products

If significant absorption of systemic atropine sulfate occurs, concurrent use of medicinal products having CNS effects, such as antiemetic agents, phenothiazines, or barbiturates, may result in opisthotonos, convulsions, coma, and extrapyramidal symptoms.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established. Animal studies are insufficient with respect to reproductive toxicity. A moderate amount of data on pregnant women indicates no malformative or feto/neonatal toxicity of atropine sulfate.

Atropine sulfate rapidly crosses the placenta. Since atropine sulfate may be systemically absorbed after ocular administration, Ryjunea should only be used if absolutely necessary, especially during the last 3 months of pregnancy.

Breast-feeding

There is insufficient information on the effects of atropine sulfate in newborns/infants.

Atropine sulfate is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ryjunea therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies do not indicate clinically-relevant effects with respect to male fertility (see section 5.3). Animal studies to evaluate effects on female fertility have not been conducted.

There are no data on the effects of atropine eye drops on human fertility.

4.7 Effects on ability to drive and use machines

Ryjunea has a moderate influence on the ability to ride bikes, drive or use machines. Instillation of Ryjunea, may induce temporary blurred vision or other visual disturbances (see section 4.8). Patients should be advised not to ride bikes, drive or use machines until their vision has cleared. This effect may last up to 14 days after stopping treatment (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are photophobia (23.4%), eye irritation (9.9%) and blurred vision (7.8%).

Tabulated list of adverse reactions

Adverse reactions reported in a phase III clinical trial where 282 patients aged 3 to 18 years were exposed to Ryjunea 0.1 mg/ml are tabulated below by system organ class and by frequency. Approximately 0.4% of patients using Ryjunea discontinued due to any adverse event in the 24-month study.

The frequencies are as follows: 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), not known (cannot be estimated from the available data).

Table 1. Adverse reactions observed in clinical trial specific for Ryjunea 0.1 mg/ml

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1 000 to <1/100
Nervous system disorders		Headache	
Eye disorders	Photophobia	Vision blurred, Eye irritation, Eye pain, Foreign body sensation in eyes, Mydriasis	Accommodation disorder, Conjunctival papillae, Punctate keratitis

Description of selected adverse reactions

Photophobia

Atropine sulfate causes photophobia by dilating the pupil and paralyzing the ciliary muscle, allowing excessive light to enter the eye and impairing its ability to adjust to bright light. Photophobia was the most commonly reported adverse reaction in clinical trials, typically presenting as mild to moderate in severity. Duration of the photophobia varied from 1 to 1 392 days (average 259 days) and usually occurred intermittently (see section 4.4).

Vision blurred

Mild or moderate blurred vision is associated with atropine sulfate (see sections 4.4 and 4.7). In approximately 69% of patients, it resolves by itself during treatment (range of duration 2 to 734 days, mean duration days 135).

Eye irritation

Signs and symptoms of eye irritation associated with atropine sulfate include also eye pruritus and ocular discomfort. These are mostly mild or moderate symptoms occurring intermittently. The duration of these reactions varied from 1 to 758 days in the clinical trial and were comparable in the vehicle group and in the atropine sulfate groups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose is unlikely to occur after ocular administration.

Symptoms

Possible symptoms of overdose can be flushing and dryness of the skin, dilated pupils with photophobia, dry mouth and tongue accompanied by a burning sensation, difficulty in swallowing, tachycardia, rapid respiration, hyperpyrexia, nausea, vomiting, hypertension, rash and excitement. Symptoms of central nervous system (CNS) stimulation include restlessness, confusion, hallucinations, paranoid and psychotic reactions, incoordination, delirium and occasionally convulsions. In severe overdose, drowsiness, stupor and CNS depression may occur with coma, circulatory and respiratory failure and death.

Treatment

If overdose with atropine sulfate occurs, treatment should be symptomatic and supportive. In ocular overdose, eyes can be rinsed with water or sodium chloride 9 mg/ml (0.9 %) solution for injection. An adequate airway should be maintained. Diazepam may be administered to control excitement and convulsions, but the risk of CNS depression should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mydriatics and cycloplegics, Anticholinergics. ATC code: S01FA01

Mechanism of action

Atropine acts as a competitive and reversible antagonist at all muscarinic acetylcholine receptors. The mechanism through which atropine retards myopia progression is not fully understood but is thought to involve stimulation of scleral remodelling/strengthening that reduces axial length and vitreous chamber depth. Published literature provides evidence that the mechanism of action of atropine in myopia and in mydriatic/cycloplegic indications, is not identical.

Pharmacodynamic effects

Atropine sulfate induces mydriasis by inhibiting the contraction of the circular sphincter muscle of the iris, allowing the radial dilator muscle to contract and dilate the pupil. It also blocks cholinergic stimulation of the ciliary muscle, leading to cycloplegia by paralyzing the muscle responsible for accommodation.

Clinical efficacy and safety

The efficacy, safety and tolerability of Ryjunea 0.1 mg/ml has been evaluated in a pivotal phase III study.

The 48-month double masked vehicle controlled phase III clinical trial (STAR study), enrolled 852 children aged 3 to 14 years inclusive, with myopia of -0.50 D to -6.0 D, who were randomised to receive Ryjunea 0.1 mg/ml, 0.3 mg/ml or placebo (vehicle). At Month 36, patients, initially randomised to Ryjunea 0.1 mg/ml or 0.3 mg/ml were randomly re-assigned in a double-masked manner to either continue with Ryjunea 0.1 mg/ml or 0.3 mg/ml or were assigned to vehicle. Participants initially randomised to vehicle were assigned to receive Ryjunea 0.3 mg/ml. Treatment compliance was greater than 97% in all treatment groups.

The Full Analysis Set (FAS) included 847 participants who received at least 1 dose of study drug. Randomisation was stratified according to age [3 to < 6 years (3.1%), 6 to < 9 (21.8%), 9 to < 12 (39.1%), and 12-14 (36%)] and baseline spherical equivalent (SE) [-0.50 D to -3.0 D (61.9%), >-3.0 D to -6.0 D (31.8%)] as measured by cycloplegic autorefraction.

Demographic characteristics were similar in all treatment groups. Overall, the mean age at baseline was 10.3 ± 2.44 years, ranging from 3 to 14 years. In all groups, there were more males (55.7%) than females (44.3%). Most participants were White (68.5%); Asian participants accounted for 17.5% of the FAS. Other baseline characteristics were similar in all treatment groups. The mean participants' baseline spherical equivalent (SE) was -2.69 ± 1.309 D and was similar between the treatment groups. Participants enrolled did not suffer from any medical condition that predisposes to degenerative myopia (eg, Marfan syndrome, Stickler syndrome) or a condition that may affect visual function or development (eg, diabetes mellitus, chromosome anomaly). Additionally, participants with amblyopia, strabismus, cataract, or primary open angle and angle closure glaucoma were excluded.

Efficacy

The primary endpoint was the difference in the mean annual progression rate (APR) of myopia through 24 months between treatment and vehicle groups in the FAS. For Ryjunea 0.1 mg/ml, a statistically significant difference of 0.132 D (95% CI: 0.061, 0.204) compared to vehicle was shown.

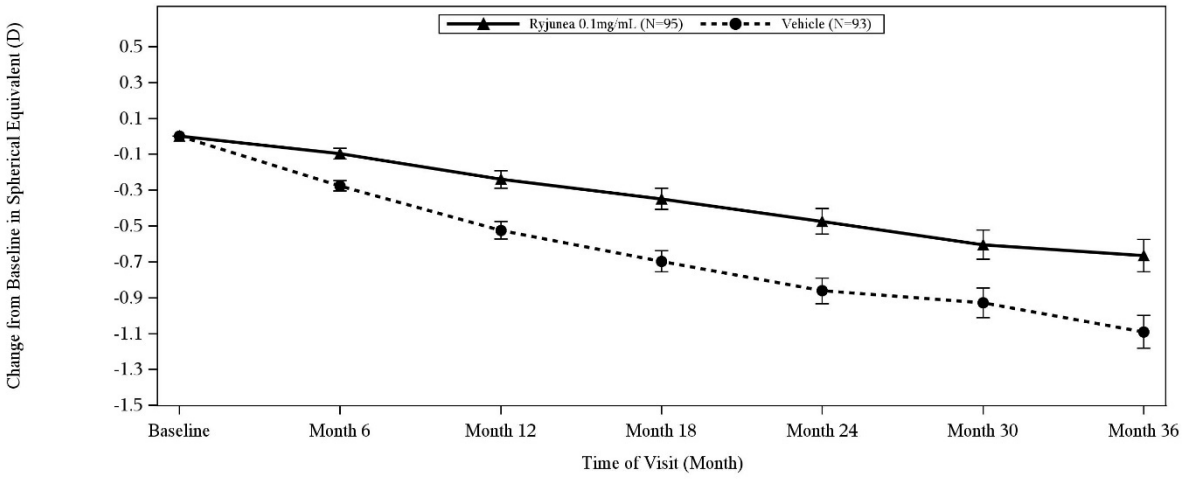
A higher treatment effect was observed in participants with progression rate of 0.5 D or more per year. In this pre-specified subgroup, a difference in mean APR of 0.207 D (95% CI: 0.112, 0.302) was observed for 0.1 mg/ml Ryjunea vs. vehicle at 24 months, and a difference in mean APR of 0.154 D (95% CI: 0.073, 0.236) was observed for 0.1 mg/ml Ryjunea vs. vehicle at 36 months. A difference in mean change from baseline spherical equivalent (SE) of 0.388 D (95% CI: 0.190, 0.585) was observed for Ryjunea 0.1 mg/ml compared to vehicle at 24 months, and a difference in mean change from baseline spherical equivalent of 0.425 D (95% CI 0.170, 0.681) was observed for Ryjunea 0.1 mg/ml compared to vehicle at 36 months (Table 2). Figure 1 shows the mean change from baseline in SE through 36 months between treatment and vehicle groups in patients with progression rate of 0.5 D or more per year.

Larger effect sizes were observed with younger ages.

Table 2: STAR-trial: Change from baseline in spherical equivalent (D) through month 36 in patients with progression rate of 0.5 D or more per year

	Vehicle (n=93)	**Ryjunea 0.1 mg/ml (n=95)**
Baseline to month 24	-0.862 (-1.00, -0.72)	-0.474 (-0.61, -0.33)
Difference to vehicle		0.388 (0.190, 0.585)
Baseline to month 36	-1.091 (-1.27, -0.91)	-0.665 (-0.85, -0.49)
Difference to vehicle		0.425 (0.170, 0.681)

Figure 1: STAR-trial: Mean change from baseline in spherical equivalent (D) through month 36 in patients with progression rate of 0.5 D or more per year



Number of Subjects							
Ryjunea 0.1mg/mL	95	82	85	85	82	76	72
Vehicle	93	85	87	81	76	70	67

In a subset of 44 participants per treatment group, there was no statistically significant improvement in axial length for Ryjunea 0.1 mg/ml compared to vehicle at month 24.

5.2 Pharmacokinetic properties

No pharmacokinetic study in paediatric patients has been performed with Ryjunea. PK data are only available for adults who received a higher dose of atropine sulfate.

Absorption

In a study of healthy subjects, after topical ocular administration of 30 µL atropine sulfate ophthalmic solution, 10 mg/ml the mean (± SD) systemic bioavailability of l-hyoscyamine was reported to be approximately 64 ± 29 %, (range 19% to 95%) as compared to intravenous administration of atropine sulfate. The mean (± SD) time to maximum plasma concentration (T_{max}) was approximately 28 ± 27 minutes (range 3 to 60 minutes), and the mean (± SD) peak plasma concentration (C_{max}) of l-hyoscyamine was 288 ± 73 pg/ml.

In a separate study of patients undergoing ocular surgery, after topical ocular administration of 40 µL of atropine sulfate ophthalmic solution, 10 mg/ml, the mean (± SD) plasma C_{max} of l-hyoscyamine was 860 ± 402 pg/ml.

Distribution

Atropine is distributed widely throughout the body and crosses the blood brain barrier. Up to 50% of the dose is protein bound.

Biotransformation

Atropine is metabolised in the liver by oxidation and conjugation to give inactive metabolites.

Elimination

The elimination half-life is about 2 to 5 hours. About 50% of the dose is excreted within 4 hours and 90% in 24 hours in the urine, about 30 to 50% as unchanged drug.

5.3 Preclinical safety data

Minimal focal hyperkeratosis of the eyelid was observed at necropsy in three of four rabbits given atropine sulfate 0.1 mg/ml eye drops three times daily.

Based of literature data, there is no evidence of mutagenic or tumorigenic effects of atropine sulfate.

Atropine sulfate administered orally reduced fertility in male rats at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Citric acid (E330)

Sodium citrate (E331)

Sodium chloride

Sodium hydroxide (E524) / hydrochloric acid (E507) (for pH adjustment)

Deuterium oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years.

After first opening: 4 weeks

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White low-density polyethylene (LDPE) 5 ml bottles with white LDPE tips and red high-density polyethylene (HDPE) screw caps with a protective tamper-evident ring.

Each multi-dose bottle contains 2.5 ml Ryjunea 0.1 mg/ml.

Pack sizes: 1 or 3 multi-dose 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 MARKETING AUTHORISATION HOLDER

Santen Oy

Niittyhaankatu 20

33720 Tampere

Finland

8 MARKETING AUTHORISATION NUMBER(S)

PL 16058/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/10/2025

10 DATE OF REVISION OF THE TEXT

24/02/2026