1. NAME OF THE MEDICINAL PRODUCT

GLAALPHA combination ophthalmic solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GLAALPHA contains 4.896 mg of ripasudil hydrochloride hydrate (4.0 mg as ripasudil) and 1.0 mg of brimonidine tartrate in 1 mL.

3. PHARMACEUTICAL FORM

Sterile aqueous ophthalmic solution
Pale yellow-green, clear liquid
pH 6.0 to 7.0
Osmotic pressure ratio of approximately 1 (ratio to isotonic sodium chloride solution)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLAALPHA is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to monotherapy.

4.2 Posology and method of administration

Posology
Use in adults, including the elderly
Instill one drop at a time, twice a day.

Use in pediatric population
No clinical studies have been conducted to evaluate the efficacy and safety in pediatric patients (see Section 4.4).

Method of Administration
(1) Route of administration: Instillation only.
(2) When dispending the drug: Instruct patients on the following:
1) In the instillation, the patient should 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

GLAALPHA is contraindicated in patients with a history of hypersensitivity to any of the components of GLAALPHA (see Section 2 and 6.1).
GLAALPHA is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

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 GLAALPHA for acute primary angle-closure glaucoma.

Conjunctival hyperaemia
In clinical studies, conjunctival hyperaemia 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, conjunctivitis (including conjunctivitis allergic) and blepharitis (including allergic blepharitis) have been reported. 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.

Systemic effects
Since GLAALPHA is absorbed systemically, adverse reactions similar to those seen with the systemic administration of α_2-adrenergic receptor agonists (e.g., sleepiness, dizziness, bradycardia, and hypotension) may occur. Accordingly, caution should be exercised.

Corneal opacity
Corneal opacity with neovascularisation, etc. may occur following administration of GLAALPHA. Patients should consult their doctor periodically, and they should be carefully monitored. In addition, they should be adequately instructed to seek medical attention immediately if they have any subjective symptoms such as hyperaemia, visual acuity reduced, or vision blurred.

Other adverse reactions
The adverse reactions listed in Section 4.8 “Undesirable effects” were observed in clinical studies. Take any appropriate measures such as discontinuation of treatment if these events occur.

Contact lenses
GLAALPHA has not been studied in patients wearing contact lenses. The preservative in GLAALPHA, benzalkonium chloride may be adsorbed by the soft contact lenses. Patients must be instructed to remove contact lenses prior to the instillation and wait at least 15 minutes after the instillation before reinserting the lenses.

Use in patients with cardiovascular diseases
Although brimonidine had minimal effect on the blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients receiving GLAALPHA with severe cardiovascular disease due to the brimonidine component.

Use in patients with other specific diseases
GLAALPHA should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension, or thromboangiitis obliterans due to the brimonidine component.

Use in pediatric population
No clinical studies have been conducted to evaluate the efficacy and safety in pediatric patients. In overseas postmarketing experience, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solution.
In an overseas clinical study, somnolence was observed at a high frequency (25% to 83%) in infants and children aged 2 to 7 years when brimonidine tartrate ophthalmic solution 0.2% was administered 3 times daily.

Decreases in corneal thickness
Corneal thickness tended to decrease in clinical studies of ripasudil hydrochloride hydrate. Decreases in corneal thickness caused by ripasudil hydrochloride hydrate were reversible.

Hepatic and renal impairment
The safety of GLAALPHA in patients with hepatic or renal impairment has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Specific medicinal product interaction studies have not been performed with GLAALPHA.
GLAALPHA is contraindicated in patients receiving monoamine oxidase inhibitors.
Concomitant administration of brimonidine tartrate ophthalmic solution with central nervous system depressants (e.g. barbiturates, opioid analgesics, sedatives or anesthetics) or alcohol is not recommended due to their potential additively-enhanced sedative effects. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives and/or cardiac glycosides is advised.
Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with GLAALPHA in humans can lead to resulting interference with the IOP lowering effect. In experiments on rabbits, however, MAO inhibitors and tricyclic antidepressants did not alter the IOP response to brimonidine.
No data on the level of circulating catecholamines after GLAALPHA administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

4.6 Fertility, pregnancy, and lactation

Fertility
There are no data on the effect of topical ocular instillation of GLAALPHA on human fertility.

Pregnancy
The safety of GLAALPHA has not been established in pregnant women. GLAALPHA should be administered to women who are or may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

Lactation
In animal studies (rats: oral administration), both ripasudil hydrochloride hydrate and brimonidine tartrate have been reported to be excreted in breast milk. Do not use GLAALPHA in breastfeeding women. If use of GLAALPHA is unavoidable, breastfeeding should be suspended.

4.7 Effects on ability to drive and use machines

Sleepiness, dizziness, and vision blurred, etc. may occur. Patients using the combination ophthalmic solution should be instructed to use caution when operating potentially hazardous machinery or driving.

4.8 Undesirable effects

In all the clinical studies, the most common adverse drug reaction was conjunctival hyperemia (53.2%). However, the symptoms were mild in severity in most cases.
Adverse reactions and frequencies observed in clinical studies are listed below by body site or by mechanism of onset of events.

	≥ 5%	0.1% to < 5%	Incidence unknown*
Hypersensitivity		Rash	Contact dermatitis, papule, erythema, urticaria
Eye	Conjunctival hyperaemia (53.2%), conjunctivitis (including conjunctivitis allergic), blepharitis (including blepharitis allergic), eye irritation	Corneal epithelium disorders (e.g., corneal erosion, punctate keratitis), keratitis, eye pruritus, erythema of eyelid, eyelid oedema, eyelid ptosis, conjunctival oedema, conjunctival follicles, conjunctival haemorrhage, keratoconjunctivitis sicca, eye discharge, eye pain, foreign body sensation in eyes, vision blurred, asthenopia, dry eye, lacrimation increased, abnormal sensation in eye	Meibomian gland obstruction, conjunctival pallor, visual disturbance, eyelid disorder, hordeolum, iritis, cataract, vitreous detachment, vitreous floaters, visual field defect, visual acuity reduced, miosis, burning sensation, photophobia, corneal opacity, intraocular pressure increased
Cardiovascular disorders		Hypotension, hypertension, palpitations	Bradycardia, tachycardia
Respiratory disorders		Cough	Nasal irritation, dyspnoea, bronchitis, pharyngitis, rhinitis, sinusitis, nasal dryness
Psychiatric and nervous system disorders		Vertigo, somnolence	Dizziness, headache, tinnitus, insomnia, depression, syncope
Gastrointestinal disorders		Dry mouth, thirst, taste abnormality	Gastrointestinal disorder, nausea
Infection			Flu syndrome, common cold, respiratory infections
Others		Asthenia	Warts, anaemia, blood bilirubin increased, blood glucose increased, blood triglycerides increased, blood uric acid increased, fatigue, hypercholesterolaemia, feels poorly

*Additional adverse reactions that have been seen with ripasudil or brimonidine and may potentially occur with GLAALPHA.

4.9 Overdose

No case of overdose of GLAALPHA has been reported and is unlikely to occur after ocular administration. If overdose occurs, treatment should be symptomatic and supportive.
If GLAALPHA is accidentally ingested the following information may be useful:

Ripasudil
No case of overdose of ripasudil has been reported during the clinical study.

Brimonidine Tartrate
In cases where brimonidine tartrate has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine tartrate overdose such as hypotension, bradycardia, hypothermia and apnoea, coma, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in a few neonates, infants, and children receiving brimonidine tartrate.
Oral overdoses of other α_2-adrenergic receptor agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics
ATC Code: S01EA55

Mechanism of Action
GLAALPHA contains two active substances: ripasudil (Rho kinases inhibitor) and brimonidine tartrate (α_2-adrenergic receptor agonist). These two components lower intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension. Although their mechanisms of action are different, these two components decrease elevated intraocular pressure by complementary mechanisms of action and the combined effect results in additional intraocular pressure reduction compared to either compound administered alone.

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 of 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 ophthalmic solution 0.4% to rabbits, the aqueous humor outflow rate was significantly increased compared to the vehicle treated group. On the other hand, the volume of uveoscleral outflow or aqueous production were not affected.

Brimonidine reduces intraocular pressure through the inhibition of aqueous humor production in the ciliary epithelium by activating the α_2-adrenergic receptor, and also promotion of aqueous humor outflow from the uveoscleral outflow pathway.
(1) Brimonidine selectively activates the α_2-adrenergic receptor rather than the α_1-adrenergic receptor.
(2) In an instillation study of brimonidine tartrate ophthalmic solution 0.2% (fluorophotometry method) into patient's eye of ocular hypertension, inhibition of aqueous humor production and increasing of aqueous humor outflow from the uveoscleral outflow pathway were observed.

Pharmacodynamic Effects
When a single dose of GLAALPHA was instilled into one eye of rabbits, an intraocular pressure-lowering effect was observed, and there was no significant difference between GLAALPHA group and the concomitant use of ripasudil ophthalmic solution 0.4% and brimonidine tartrate ophthalmic solution 0.1%.

Clinical efficacy
Phase 3 Controlled comparative study with ripasudil ophthalmic solution
In a randomized, double-masked parallel-group study using ripasudil ophthalmic solution 0.4% as the control, 1 drop of GLAALPHA or the control drug was instilled into both eyes twice a day for 8 weeks in Japanese patients with primary open-angle glaucoma (in a broad sense) or ocular hypertension with intraocular pressure ≥18 mm Hg after the instillation of ripasudil ophthalmic solution 0.4% for at least 4 weeks. The changes in intraocular pressure are shown in the following Figure 1 and Table 1, and the superiority of GLAALPHA group to the control group was demonstrated.

Figure 1 Changes in Intraocular Pressure Over Time (2 Hours After Instillation)

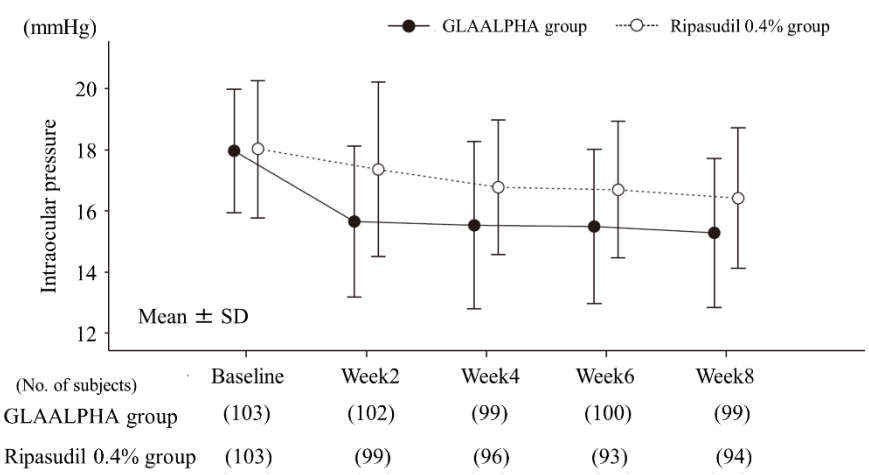


Table 1 Comparison of Changes in Intraocular Pressure 2 Hours After Instillation (mm Hg)

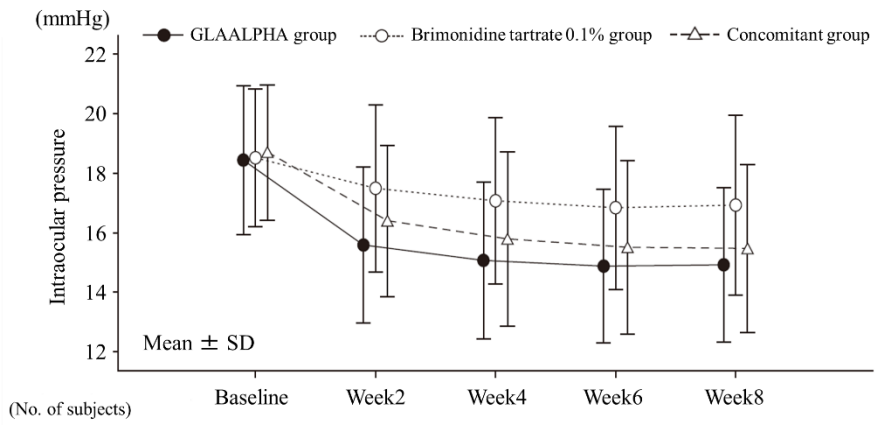
	Change in intraocular pressure
GLAALPHA group (n = 100)	-2.57 ± 0.144 [-2.85, -2.29]
Ripasudil 0.4% group (n = 96)	-1.17 ± 0.147 [-1.46, -0.88]
Difference between groups	-1.40 ± 0.206** [-1.81, -1.00]

Least-square mean ± SE, [95% confidence interval]
Primary endpoint: Changes in intraocular pressure from baseline to 3 timepoints (Weeks 4, 6, and 8) at 2 hours after instillation
** $p \leq 0.01$ (Repeated measures ANOVA at 3 timepoints)

The incidence of adverse reactions was 53.4% (55/103 subjects) in the combination ophthalmic solution group. The most common adverse reaction was conjunctival hyperaemia in 43.7% (45/103 subjects). Other than conjunctival hyperaemia, adverse reactions with at least 2 incidents were eye irritation in 8.7% (9/103 subjects), eye discharge in 1.9% (2/103 subjects), and somnolence in 1.9% (2/103 subjects).

Phase 3 Controlled comparative study with brimonidine ophthalmic solution
In a randomized, single-mask (assessor-masked) parallel-group study using brimonidine tartrate ophthalmic solution 0.1% as the control, 1 drop of GLAALPHA or the control drug was instilled into both eyes twice a day for 8 weeks in Japanese patients with primary open-angle glaucoma (in a broad sense) or ocular hypertension with intraocular pressure ≥18 mm Hg after the instillation of brimonidine tartrate ophthalmic solution 0.1% for at least 4 weeks. The changes in intraocular pressure are shown in the following Figure 2 and Table 2, and the superiority of GLAALPHA group to the control group was demonstrated.
In addition, the intraocular pressure-lowering effect of GLAALPHA was similar to that of the co-administration of ripasudil ophthalmic solution 0.4% and brimonidine tartrate ophthalmic solution 0.1%.

Figure 2 Changes in Intraocular Pressure Over Time (2 Hours After Instillation)



(No. of subjects)	Baseline	Week2	Week4	Week6	Week8
GLAALPHA group	(113)	(111)	(111)	(111)	(110)
Brimonidine tartrate 0.1% group	(113)	(113)	(113)	(112)	(112)
Concomitant group	(56)	(55)	(56)	(53)	(54)

Table 2 Comparison of Changes in Intraocular Pressure 2 Hours After Instillation (mm Hg)

	Change in intraocular pressure
GLAALPHA group (n = 111)	-3.36 ± 0.166 [-3.69, -3.04]
Brimonidine tartrate 0.1% group (n = 113)	-1.53 ± 0.165 [-1.86, -1.21]
Difference between groups	-1.83 ± 0.234** [-2.29, -1.37]

Least squares mean ± SE, [95% confidence interval]
Primary endpoint: Changes in intraocular pressure from baseline to 3 timepoints (Weeks 4, 6, and 8) at 2 hours after instillation
** $p \leq 0.01$ (Repeated measures ANOVA at 3 timepoints)

The incidence of adverse reactions was 55.8% (63/113 subjects) in the combination ophthalmic solution group. The most common adverse reaction was conjunctival hyperaemia in 54.0% (61/113 subjects). Other than conjunctival hyperaemia, adverse reactions with at least 2 incidents were eye irritation in 5.3% (6/113 subjects) and blepharitis in 1.8% (2/113 subjects).

5.2 Pharmacokinetic properties

Plasma Concentration and Urinary Excretion
When GLAALPHA, ripasudil ophthalmic solution 0.4% or brimonidine tartrate ophthalmic solution 0.1% was instilled repeatedly to 17 Japanese healthy male adults at a dose of 1 drop/eye in both eyes twice a day for 8 days in a 3-group, 3-period crossover design, pharmacokinetic parameters of unchanged ripasudil, its main metabolite M1 (isoquinoline ring position 1 hydroxylated form), and unchanged brimonidine were as shown in the following Table 3 and Table 4.

Table 3 Plasma Pharmacokinetic Parameters After Repeated Instillation in Healthy Male Adults (Ripasudil and Metabolite M1)

Instillation group (Components to be measured)	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
GLAALPHA (ripasudil)	0.4137 ± 0.2583	0.1387 ± 0.1103	0.083 [0.08, 0.25]	0.325
Ripasudil 0.4% (ripasudil)	0.7958 ± 0.6263	0.2250 ± 0.1820	0.083 [0.08, 0.25]	0.250
GLAALPHA (ripasudil metabolite M1)	0.8177 ± 0.4088	2.7856 ± 1.4549	0.500 [0.50, 1.00]	3.096 ± 0.569
Ripasudil 0.4% (ripasudil metabolite M1)	1.0741 ± 0.5466	3.3695 ± 2.0076	0.500 [0.50, 0.50]	3.264 ± 1.181

C_{max}, $AUC_{0-\tau}$, $t_{1/2}$: mean ± SD
t_{max}: median [minimum, maximum]
n = 17 (n = 1 only for $t_{1/2}$ of ripasudil)

Table 4 Plasma Pharmacokinetic Parameters After Repeated Instillation in Healthy Male Adults (Brimonidine)

Instillation group (Components to be measured)	C_{max} (pg/mL)	$AUC_{0-\tau}$ (pg·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
GLAALPHA (brimonidine)	38.011 ± 19.886	66.826 ± 31.274	0.083 [0.08, 0.25]	1.903 ± 0.592
Brimonidine tartrate 0.1% (brimonidine)	24.043 ± 8.912	83.365 ± 32.170	0.500 [0.25, 1.00]	2.087 ± 0.661

C_{max}, $AUC_{0-\tau}$, $t_{1/2}$: mean ± SD
t_{max}: median [minimum, maximum]
n = 17

Entry into the Ocular Tissues
A single dose of ripasudil ophthalmic solution 0.4%, brimonidine tartrate ophthalmic solution 0.1%, or GLAALPHA (50 μL each) was instilled to both eyes of male pigmented rabbits.
The ripasudil concentration in the aqueous humor after instillation of GLAALPHA was higher for $AUC_{0-\tau}$ than that after instillation of ripasudil ophthalmic solution 0.4% (approximately 1.8 times). In addition, brimonidine concentration in the aqueous humor was lower for C_{max} and $AUC_{0-\tau}$ after instillation of GLAALPHA than that after instillation of brimonidine tartrate ophthalmic solution 0.1% (approximately 0.2 times and 0.6 times, respectively).
The ripasudil concentration in the iris/ciliary body after instillation of GLAALPHA was higher for C_{max} than that after instillation of ripasudil ophthalmic solution 0.4% (approximately 1.8 times). In addition, brimonidine concentration in the iris/ciliary body after instillation of GLAALPHA was lower for C_{max} and $AUC_{0-\tau}$ than that after instillation of brimonidine tartrate ophthalmic solution 0.1% (approximately 0.4 times and 0.6 times, respectively).

5.3 Preclinical safety data

Ripasudil
In a 13-week repeated instillation study of ripasudil ophthalmic solution in rabbits receiving 2.0% (twice a day) and a 13-week repeated instillation study of ripasudil ophthalmic solution in dogs receiving 4.0% (4 times daily), irreversible degeneration of fiber with opacity was observed in the suture line of the anterior part of the lens. Such changes in the lens are thought to be caused by the inhibition of formation of actin stress fibers by the Rho kinase inhibiting effect of ripasudil hydrochloride hydrate, which leads to the inhibition of differentiation into the lens fiber cells and subsequent elongation and migration.
Brimonidine
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and a 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 120 times, respectively, the plasma C_{max} drug concentration in humans treated with one drop of brimonidine tartrate ophthalmic solution, 0.1% into both eyes 3 times per day, the recommended daily human dose.
Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberration assay in Chinese hamster ovary (CHO) cells, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenic assay, and dominant lethal assay.
Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses which achieve up to approximately 125 times the systemic exposure by C_{max} following the maximum recommended human ophthalmic dose of brimonidine tartrate ophthalmic solution 0.1%.
Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg/kg/day) and rabbits (5.0 mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, respectively, than similar values estimated in humans treated with brimonidine tartrate ophthalmic solution 0.1%, 1 drop in both eyes three times daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate, sodium chloride, sodium hydroxide, benzalkonium chloride concentrated solution 50, purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30ºC. Discard four weeks after first opening.

6.5 Nature and contents of container

A brown polypropylene bottle containing ultraviolet absorber with a low-density polyethylene inner plug and a polypropylene cap containing 5 mL ophthalmic solution. A carton contains 1 bottle.

7. PRODUCT OWNER

Name: Kowa Company, Ltd.
Address: 6-29, Nishiki 3-chome, Naka-ku, Nagoya, Aichi, JAPAN

8. DATE OF REVISION OF THE TEXT

2 June, 2025