Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRINLOTAN CO eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains latanoprost 50 micrograms and timolol maleate 6,8 mg equivalent to 5 mg timolol.

Excipients with known effect:

Benzalkonium chloride 0,02 % *m/v*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

The solution is a clear, free from particles, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are not controlled on, or are intolerant to, monotherapy with compounds other than latanoprost and timolol.

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4.2 Posology and method of administration

Posology

Adults (including the elderly)

One drop in the effected eye(s) once daily.

The dosage of TRINLOTAN CO should not exceed once daily since it has been shown that more frequent administration of latanoprost decreases the intraocular pressure lowering effect.

If one dose is missed, treatment should continue with the next dose as planned.
When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced.

Paediatric population

The safety and efficacy of TRINLOTAN CO in children has not yet been established.

Method of administration

For ophthalmic use.

The screwcap should be removed before use.

If more than one topical ophthalmic medicine is being used, the medicines should be administered at least five minutes apart.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Bronchial asthma or a history of bronchial asthma, chronic obstructive pulmonary disease (COPD).
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block (not controlled with pace-maker), cardiac failure, cardiogenic shock.

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- Active herpes simplex keratitis or recurrent herpetic keratitis specifically associated with prostaglandin analogues (see section 4.4).

4.4 Special warnings and precautions for use

Latanoprost

Iris pigmentation changes

Latanoprost may gradually increase the brown pigment of the iris. The eye colour change is due to increased melanin content in the stromal melanocytes of the iris, rather than to an increase in the number of melanocytes. 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. The change in iris colour is mild in the majority of cases and may not be detected clinically. The increase in iris pigmentation in one or both eyes has been documented predominantly in patients who have mixed colour irides that contain the colour brown at baseline. Neither nevi nor freckles of the iris have been affected by treatment. No accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has been observed in clinical trials.

In a clinical trial designed to assess iris pigmentation over five years, there was no evidence of adverse consequences due to increased pigmentation even when administration of latanoprost continued. These results are consistent with post-marketing clinical experience since 1996. In addition, IOP reduction was similar in patients regardless of the development of increased iris pigmentation. Therefore, treatment with latanoprost can be continued in patients who develop increased iris pigmentation. These patients should be examined regularly and, depending on the clinical situation, treatment may be stopped.

Onset of increased iris pigmentation typically occurs within the first year of treatment, rarely during the second or third year, and has not been seen 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. During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of

treatment, but the resultant colour change may be permanent.

Eyelid and eyelash changes

Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost.

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

The potential for heterochromia exists for patients receiving unilateral treatment.

Macular oedema

Macular oedema, including cystoid macular oedema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule, or in patients with known risk factors for macular oedema. Caution is recommended when using TRINLOTAN CO in these patients.

Glaucoma

There is no documented experience with latanoprost-timolol in inflammatory, neovascular, chronic angle closure or congenital glaucoma, in open-angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Therefore, it is recommended that TRINLOTAN CO should be used with caution in these conditions until more experience is obtained.

Herpetic keratitis

Latanoprost should be used with caution in patients with a history of herpetic keratitis and is contraindicated in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues (see section 4.3).

Timolol

Systemic effects

The same adverse reactions found with systemic administration of beta-adrenergic blocking medicines may occur with their topical administration. Patients with a history of severe cardiac

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disease should be monitored closely for signs of cardiac failure. The following cardiac and respiratory reactions may occur after topical application of timolol maleate as in TRINLOTAN CO:

• Aggravation of Prinzmetal's angina.

• Aggravation of peripheral and central circulatory disorders.

• Hypotension.

• Cardiac failure resulting in death.

• Severe respiratory reactions, including fatal bronchospasm in patients with asthma.

• Bradycardia.

Cardiac disorders

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

The concomitant use of TRINLOTAN CO with hypoglycaemic medicines, phenothiazines and various anti-dysrhythmic medicines may have interactions with life-threatening consequences.

A gradual withdrawal of beta-adrenergic blocking medicines prior to major surgery should be considered. Beta-adrenergic blocking medicines impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, which may augment the risk of general anaesthesia in surgical procedures. Protracted severe hypotension during anaesthesia and difficulty restarting and maintaining the heartbeat have been reported. During surgery, the effects of beta-adrenergic blocking medicines may be reversed by sufficient doses of adrenergic agonists.

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving timolol.

Hypoglycaemia/diabetes

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Beta-adrenergic blocking medicines may increase the hypoglycaemic effect of medicines used to treat diabetes and mask the signs and symptoms of hypoglycaemia. They should be used with caution in patients with spontaneous hypoglycaemia or diabetes (especially those with labile diabetes), who are receiving insulin or oral hypoglycaemic medicines.

Therapy with beta-adrenergic blocking medicines may mask certain signs and symptoms of hyperthyroidism. Abrupt withdrawal of therapy may precipitate a worsening of this condition.

Anaphylactic reactions

When treated with beta-adrenergic blocking medicines, patients with a history of atopy or severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens. They may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

Myasthenia gravis or myasthenic symptoms

Timolol maleate has been reported to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms (e.g. diplopia, ptosis, generalised weakness).

Choroidal detachment

Choroidal detachment after filtration procedures has been reported with the administration of ocular hypotensive medicines.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Benzalkonium chloride

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. 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.

As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride-preserved

ophthalmological preparations cannot be excluded, regular ophthalmological examination is required.

Caution should be exercised in the use of benzalkonium chloride-preserved topical medicine over an extended period in patients with extensive ocular surface disease.

Preservative

TRINLOTAN CO contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of TRINLOTAN CO in dry eye patients, or in conditions where the cornea is compromised.

Contact lenses

Contact lenses may absorb benzalkonium chloride and these should be removed before applying TRINLOTAN CO but may be reinserted after 15 minutes.

Timolol may interact with other medicines, see section 4.5.

Paediatric population

Safety and effectiveness in children have not been established.

4.5 Interactions with other medicines and other forms of interaction

Specific interaction studies have not been performed with TRINLOTAN CO.

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when TRINLOTAN CO is given to patients already receiving an oral beta-adrenergic blocking medicine.

The use of two or more topical beta-adrenergic blocking medicines is not recommended.

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There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogs. Therefore, the use of two or more prostaglandins, prostaglandin analogs, or prostaglandin derivatives is not recommended.

The potential exists for additive effects resulting in hypotension and/or marked bradycardia when eye drops containing timolol are administered with calcium-channel blockers, catecholamine-depleting medicines or beta-blocking medicines, anti-arrhythmics (including amiodarone and quinidine), digitalis glycosides, parasympathomimetics, narcotics and monoamine oxidase (MAO) inhibitors.

Potentiated systemic beta blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis has occasionally been reported when timolol is given with adrenaline, although TRINLOTAN CO alone has little or no effect on pupil size.

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic medicines (see section 4.4).

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

The concomitant use of TRINLOTAN CO with hypoglycaemic medicines, phenothiazines and various anti-arrhythmic medicines may have interactions with life-threatening consequences.

Paediatric population

No information available.

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4.6 Fertility, pregnancy and lactation

Pregnancy

The safety in pregnancy has not been established.

Breastfeeding

TRINLOTAN CO should not be used in women who are breastfeeding their infants. Breastfeeding should be stopped as timolol is excreted into breast milk and latanoprost and its metabolites may pass into breast milk.

Fertility

Neither Latanoprost nor timolol have been found to have any effect on male or female fertility.

4.7 Effects on ability to drive and use machines

TRINLOTAN CO has minor influence on the ability to drive and use machines. Instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

It is not always possible to predict to what extent TRINLOTAN CO may interfere with the daily activities of a patient.

Patients should ensure that they do not engage in the above activities until they are aware of the measure to which TRINLOTAN CO affects them.

4.8 Undesirable effects

a. Summary of the safety profile

For latanoprost, the majority of adverse reactions relate to the ocular system. In data from the extension phase of the latanoprost and timolol, 16 – 20 % of patients developed increased iris

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pigmentation, which may be permanent. In an open 5-year latanoprost safety study, 33 % of patients developed iris pigmentation (see section 4.4).

The most frequent findings of increased iris pigmentation were in patients with green-brown, yellow-brown and blue/grey/brown irides. In patients with homogenously blue, grey, green or brown eyes, the change was only rarely seen.

Darkening, thickening and lengthening of the eye lashes has been reported.

Other ocular adverse reactions are generally transient and occur on dose administration.

Undesirable effects which may occur frequently (usually transient ocular effects) are irritation of the eye, including stinging, burning and itching, eye hyperaemia, corneal disorders, conjunctivitis, blepharitis, eye pain, headache and skin rash.

For timolol, the most serious adverse reactions are systemic in

nature, including bradycardia, dysrhythmia, congestive heart failure, bronchospasm and allergic reactions.

Like other topically applied ophthalmic medicines, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta blocking medicines. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

b. Tabulated summary of adverse reactions

Latanoprost / Timolol

System Organ Class	Frequency	Adverse Event
Infections and infestations	Frequent	Infection; sinusitis; upper respiratory tract infection.
Metabolism and nutrition disorders	Frequent	Diabetes mellitus; hypercholesterolemia.

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Psychiatric disorders	Frequent	Depression.
Nervous system disorders	Frequent	Headache.
Eye disorders	Frequent	Hypertrichosis (eyelash and vellus hair changes of the eyelids; increased length, thickness, pigmentation, and number of eyelashes); abnormal vision; blepharitis; cataract; conjunctival disorder; conjunctivitis; corneal disorder; errors of refraction; eye hyperaemia; eye irritation (including stinging, burning, itching, foreign body sensation); eye pain; increased iris pigmentation; keratitis; photophobia; visual field defect.
Vascular disorders	Frequent	Hypertension.
Skin and subcutaneous tissue disorders	Frequent	Rash; skin disorder.
	Less frequent	Pruritis.
Musculoskeletal and connective tissue disorders	Frequent	Arthritis.

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Latanoprost

System Organ Class	Frequency	Adverse Event
Infections and infestations	Frequency unknown	Herpetic keratitis.
Nervous system disorders	Frequency unknown	Dizziness.
Eye disorders	Frequent	Eye irritations (burning, grittiness, itching, stinging, and foreign body sensation); eyelid oedema; transient punctate epithelial erosions; punctate keratitis.
	Frequency unknown	Corneal oedema and erosions; eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); iris cyst; iritis; macular oedema including cystoid macular oedema; dry eye; misdirected eyelashes sometimes resulting in eye irritation; periorbital and lid changes resulting in deepening of the eyelid sulcus; periorbital oedema;

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		photophobia; pseudopemphigoid of the ocular conjunctiva*; trichiasis; uveitis; vision blurred.
Cardiac disorders	Frequency unknown	Angina; unstable angina; palpitations.
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Acute asthma attacks; asthma; asthma aggravation; dyspnoea.
Skin and subcutaneous tissue disorders	Frequent	Skin rash.
	Frequency unknown	Darkening of palpebral skin of the eyelids; localised skin reaction on eyelids.
Musculoskeletal and connective tissue disorders	Frequency unknown	Arthralgia; myalgia.
General disorders and administration of site conditions	Frequency unknown	Non-specific chest pain.

* May be potentially related to the preservative benzalkonium chloride.

Timolol maleate (Ocular Administration)

System Organ Class	Frequency	Adverse Event
Immune system disorders	Frequency unknown	Signs and symptoms of systemic allergic reactions including anaphylaxis,

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		angioedema, localised and generalised rash, pruritus and urticaria.
Metabolism and nutrition disorders	Frequency unknown	Anorexia; masked symptoms of hypoglycaemia in diabetic patients.
Psychiatric disorders	Frequency unknown	Behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; depression; insomnia; nightmares.
Nervous system disorders	Frequency unknown	Dizziness; paraesthesia; somnolence; cerebral ischaemia; cerebral vascular accident; increase in signs and symptoms of myasthenia gravis; syncope; headache.
Eye disorders	Frequency unknown	Choroidal detachment following filtration surgery; corneal erosion; keratitis; cystoid macular oedema; decreased corneal sensitivity; diplopia; ptosis; signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing,

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		redness); dry eyes; visual disturbance including refractive changes; blepharitis; blurred vision.
Ear and labyrinth disorders	Frequency unknown	Tinnitus.
Cardiac disorders	Frequency unknown	Bradycardia; cardiac arrest; cardiac failure; atrioventricular block; congestive heart failure; chest pain; oedema; dysrhythmia; palpitations; heart block; worsening of angina pectoris.
Vascular disorders	Frequency unknown	Claudication; cold hands and feet; hypotension; Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Bronchospasm (predominately in patients with pre-existing bronchospastic disease); cough; dyspnoea; nasal congestion; pulmonary oedema; respiratory failure.
Gastrointestinal Disorders	Frequency unknown	Abdominal pain; diarrhoea; dry mouth; dysgeusia; dyspepsia; nausea; retroperitoneal fibrosis; vomiting.

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Skin and subcutaneous tissue disorders	Frequency unknown	Alopecia; pseudopemphigoid; psoriasiform; skin rash; exacerbation of psoriasis.
Musculoskeletal and connective tissue disorders	Frequency unknown	Myalgia, systemic lupus erythematosus.
Reproductive system and breast disorders	Frequency unknown	Decreased libido; impotence; Peyronie's disease; sexual dysfunction.
General disorders and administration of site conditions	Frequency unknown	Asthenia; fatigue.

Cases of corneal calcification have been reported in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

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. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are known if latanoprost is overdosed. Symptoms of systemic timolol overdosage are bradycardia, hypotension, bronchospasm and cardiac arrest.

If such symptoms occur, the treatment should be symptomatic and supportive.

If latanoprost is accidentally ingested, the following may be useful: One 2,5 mL bottle contains 125 micrograms latanoprost. More than 90 % is metabolised during the first pass through the liver. Intravenous infusion of 3 µg/kg in healthy volunteers induced no symptoms, but a dose of 5,5 – 10 µg/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating.

In patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost such as included in TRINLOTAN CO when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost. Studies have shown that timolol does not dialyse readily.

There have been reports of inadvertent overdosage with TRINLOTAN CO resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking medicines such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest.

Paediatric population

No data are available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals – Beta blocking agents – timolol, combinations

ATC code: S01ED51

Category and class: A 15.4 Ophthalmic preparations: Others

Mechanism of action

TRINLOTAN CO consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action.

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Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a prostanoid selective prostaglandin F_2 (FP) receptor agonist that reduces the IOP by increasing the outflow of aqueous humour.

The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow activity (decrease in trabecular outflow resistance) has been reported.

Latanoprost has no significant effect on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.

Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking medicine. Timolol lowers IOP by decreasing aqueous humour formation in the ciliary epithelium. The precise mechanism of action has not been clearly established.

Onset of action of TRINLOTAN CO is within one hour, and maximal effect occurs within six to eight hours. IOP reducing effect has been shown to be present up to 24 hours post dosage after multiple treatments.

5.2 Pharmacokinetic properties

Latanoprost

Latanoprost is an isopropyl ester prodrug that is inactive, but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea and all medicine that enters the aqueous humour is hydrolysed during the passage through the cornea. The maximum concentration in the aqueous humour, approximately 30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone.

The acid of latanoprost has a plasma clearance of 0,4 L/h/kg and a small volume of distribution, 0,16 L/kg, resulting in a rapid half-life in plasma of 17 minutes.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity and are excreted primarily in the urine.

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Timolol

The maximum concentration of timolol in the aqueous humour is reached about one hour after topical administration of eye drops. Part of the dose is absorbed systemically, and a maximum plasma concentration of 1 ng/mL is reached 10 – 20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day). The half-life of timolol in plasma is about 4 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.

Latanoprost / Timolol as in TRINLOTAN CO

No pharmacokinetic interactions between latanoprost and timolol were observed, although there is a tendency for increased concentrations of the acid of latanoprost in aqueous humour 1 to 4 hours after administration of TRINLOTAN CO compared to monotherapy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Disodium phosphate dodecahydrate

Sodium chloride

Sodium dihydrogen phosphate dihydrate

Sodium hydroxide or hydrochloric acid

Purified water

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with latanoprost eye drops. If

such medicines are used concomitantly with TRINLOTAN CO, the eye drops should be administered with an interval of at least five minutes.

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6.3 Shelf life

Shelf life: 3 years.

After opening of the eye drop container: 28 days (4 weeks)

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC) in the original carton. Once the bottle is opened the contents must be used within 28 days and may be stored at room temperature at or below 25 ºC.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

The drops are available in a 5 mL multidose, transparent LDPE bottles with a white HDPE screw cap and a transparent LDPE dropper insert.

Each bottle contains 2,5 mL or 3 mL eye drop solution. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

TRINOPTHAL CO 54/15.4/0395 (Master)

TANOTRIN CO 54/15.4/0396.394 (Duplicate)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 June 2025

10. DATE OF REVISION OF THE TEXT

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