PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF MEDICINE
OPTURAN (Ophthalmic Solution)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml of ophthalmic solution contains 40 µg travoprost and 5 mg timolol (as timolol maleate).
Excipient with known effect:
Each 1 ml ophthalmic of solution contains 150 µg benzalkonium chloride and 5 mg macrogolglycerol hydroxystearate 40, see section 4.4.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Ophthalmic solution.
Clear, colourless, aqueous solution, practically free from particles.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Decrease of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma for whom treatment with either travoprost or timolol given alone provides insufficient IOP reduction.

4.2 Posology and method of administration
Posology
Use in adults, including the elderly
The dose is one drop of OPTURAN in the conjunctival sac of the affected eye(s) once daily, in the morning or in the evening.

OPTURAN should be used at the same time each day. Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of OPTURAN administered via the ocular route and result in a decrease in systemic side-effects.
If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart (see section 4.5).

If a dose is missed, treatment should continue with the next dose as planned.
The dose should not exceed one drop in the affected eye(s) daily. When substituting another ophthalmic antiglaucoma medicine with OPTURAN, discontinue the other medicine and start the following day with OPTURAN.

Special populations
Use in children and adolescents
The efficacy and safety of OPTURAN in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data becomes available.

Use in hepatic and renal impairment
No studies have been conducted with OPTURAN eye drops in patients with hepatic or renal impairment. Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment was necessary in these patients.
Method of administration
For ocular use only.
The patient should remove the protective overwrap immediately prior to initial use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.
Patients should be instructed to:
- Wash their hands carefully prior to instillation.
- Throw away the eye drop container after 28 days after first opening (see section 6.3).

Patients must be instructed to remove soft contact lenses prior to application of OPTURAN and wait 15 minutes after instillation of the dose before reinsertion (see section 4.4).

4.3 Contraindications
OPTURAN is contraindicated in:
- Hypersensitivity to travoprost, timolol, beta blockers or to any of the excipients listed in section 6.1;
- Patient diagnosed with:
  - Bronchial asthma or a history of bronchial asthma.
  - Severe chronic obstructive pulmonary disease.
  - Sinus bradycardia.
  - Sick sinus syndrome, including sino-atrial block.
  - Second or third-degree atrioventricular block.
  - Overt cardiac failure.
  - Cardiogenic shock.
  - Severe allergic rhinitis.
  - Corneal dystrophies.

4.4 Special warnings and precautions for use
Systemic effects
OPTURAN is absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-adrenergic blocking medicines may occur. Cardiac failure should be adequately controlled before beginning therapy with timolol as in OPTURAN. Patients with a history of severe cardiac disease should be observed for signs of cardiac failure and have their pulse rates checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failures, have been reported following administration of timolol maleate. OPTURAN should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta adrenergic blocking medicines may mask the signs and symptoms of, and the response to hypoglycaemia. It may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, peripheral and central circulatory disorders and hypotension.

Cardiac disorders
In patients with cardiovascular diseases (e.g., coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions. Due to their 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.
Respiratory disorders
Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of some ophthalmic beta blockers. OPTURAN should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD).

Hypoglycaemia/diabetes
Beta blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or in patients with labile diabetes, as beta blockers may mask the signs and symptoms of acute hypoglycaemia.

Muscle weakness
Beta-adrenergic blocking medicines have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalised weakness).

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

Choroidal detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide) after filtration procedures.
Other beta-blocking medicines
The effect on intra-ocular pressure or the known effects of systemic beta blockade may be potentiated when timolol is given to patients already receiving a systemic beta-blocking medicine. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking medicines is not recommended (see section 4.5).
Surgical anaesthesia
Beta-blocking ophthalmological preparations may block systemic beta-agonist effects, e.g., of adrenaline. The anaesthetist should be informed when the patient is receiving timolol.

Skin contact
Prostaglandins and prostaglandin analogues are biologically active substances that may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.

Anaphylactic reactions
While using OPTURAN, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy
Timolol may interact with other medicines. The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when OPTURAN is given to patients already receiving an oral beta-blocking medicine. The use of two local beta-adrenergic blocking medicines or two local prostaglandins is not recommended.
Ocular effects
Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has predominantly been seen in patients with mixed coloured irises, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.

Travoprost may gradually change eyelashes of the treated eye(s). These changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation and/or number of lashes. The mechanism of eyelash changes and their long-term consequences are currently unknown.

Travoprost has been shown to cause slight enlargement of the palpebral fissure in studies in the monkey. However, this effect was not observed during clinical trials and is considered to be species specific.

There is no experience of OPTURAN in inflammatory ocular conditions, nor in neovascular angle-closure, narrow-angle or congenital glaucoma and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma.

Caution is recommended when using OPTURAN in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

In patients with known predisposing risk factors for iritis/uveitis, OPTURAN can be used with caution.

Excipients
OPTURAN contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Patients must be instructed to remove contact lenses prior to application of OPTURAN and wait at least 15 minutes after instillation of the dose before reinsertion (see section 4.2). OPTURAN also contains macrogolglycerol hydroxystearate 40 which may cause skin reactions.

4.5 Interaction with other medicines and other forms of interaction
Interactions of OPTURAN with other medicines have not been specifically evaluated.
There is a potential for additive effects resulting in hypotension and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, or beta-blocking medicines, antidysrhythmics, digoxin or parasympathomimetics.

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

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 resulting from concomitant use of ophthalmic beta blockers and adrenaline (epinephrine) has been reported occasionally.

Beta-blockers such as timolol contained in OPTURAN may increase the hypoglycaemic effect of antidiabetic medicines and may mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6 Fertility, pregnancy and lactation
Women of childbearing potential
OPTURAN must not be used in women who may become pregnant unless adequate contraceptive measures are in place.
Pregnancy
Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/newborn child. Timolol as in OPTURAN should not be used during pregnancy.
There are no adequate data from the use of OPTURAN in pregnant women. Animal studies with travoprost have shown reproductive toxicity. OPTURAN should not be used during pregnancy.
Breastfeeding
It is unknown whether travoprost from eye drops is excreted in human breast milk.
Timolol is excreted in breast milk and has the potential to cause serious adverse reactions in the breast-fed infant. Therefore, mothers breastfeeding their babies should not be treated with OPTURAN.

4.7 Effects on ability to drive and use machines
Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery. OPTURAN may also cause hallucinations, dizziness, nervousness and/or fatigue (see section 4.8) which may affect the ability to drive and use machines.

4.8 Undesirable effects
a. Tabulated summary of adverse reactions for travoprost

System Organ Class	Frequency	Undesirable effect
Immune system disorders	Frequency unknown	Seasonal allergy.
Psychiatric disorders	Frequency unknown	Anxiety, insomnia.
Eye disorders	Frequency unknown	Uveitis, conjunctival follicles, eye discharge, periorbital oedema, eyelids pruritus, ectropion, cataract, iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, halo vision, hypoaesthesia eye, anterior chamber pigmentation, mydriasis, eyelash hyperpigmentation, eyelash thickening, visual field defect.
Ear and labyrinth disorders	Frequency unknown	Vertigo, tinnitus.
Vascular disorders	Frequency unknown	Blood pressure diastolic decreased, blood pressure systolic increased.
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Asthma aggravated, rhinitis allergic, epistaxis, respiratory disorder, nasal congestion, nasal dryness.
Gastrointestinal disorders	Frequency unknown	Peptic ulcer reactivated, gastrointestinal disorder, diarrhoea, constipation, dry mouth, abdominal pain, nausea, vomiting.
Skin and subcutaneous tissue disorders	Frequency unknown	Skin exfoliation, hair texture abnormal, dermatitis allergic, hair colour changes, madarosis, pruritus, hair growth abnormal, erythema.
Musculoskeletal and connective tissue disorders	Frequency unknown	Musculoskeletal pain, arthralgia.
Renal and urinary disorders	Frequency unknown	Dysuria, urinary incontinence.
General disorders and administration site conditions	Frequency unknown	Asthenia.
Investigations	Frequency unknown	Prostatic specific antigen increased.

b. Tabulated summary of adverse reactions for timolol

System Organ Class	Frequency	Undesirable effect
Immune system disorders	Frequency unknown	Systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritus, anaphylaxis.
Metabolism and nutrition disorders	Frequency unknown	Hypoglycaemia.
Psychiatric disorders	Frequency unknown	Hallucinations, insomnia, nightmares, memory loss.
Nervous system disorders	Frequency unknown	Cerebral ischaemia, increases in signs and symptoms of myasthenia gravis.
Eye disorders	Frequency unknown	Signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing, redness), choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, diplopia.
Cardiac disorders	Frequency unknown	Oedema, congestive heart failure, atrioventricular block, cardiac arrest.
Vascular disorders	Frequency unknown	Raynaud's phenomenon, cold hands and feet.
Gastrointestinal disorders	Frequency unknown	Nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.
Skin and subcutaneous tissue disorders	Frequency unknown	Psoriasiform rash or exacerbation of psoriasis.
Musculoskeletal and connective tissue disorders	Frequency unknown	Myalgia.
Reproductive system and breast disorders	Frequency unknown	Sexual dysfunction, decreased libido.
General disorders and administration site conditions	Frequency unknown	Asthenia.

c. Tabulated summary of adverse reactions for OPTURAN

System Organ Class	Frequency	Undesirable effect
Immune system disorders	Less Frequent	Hypersensitivity.
Psychiatric disorders	Less Frequent	Nervousness.
	Frequency unknown	Hallucinations*, depression.
Nervous system disorders	Less Frequent	Headache, dizziness.
	Frequency unknown	Cerebrovascular accident, syncope, paraesthesia.
Eye disorders	Frequent	Eye pain, eye irritation, foreign body sensation in eyes, dry eye, eye pruritus, conjunctival hyperaemia, ocular hyperaemia, punctate keratitis, visual disturbance, blurred vision, ocular discomfort.
	Less Frequent	Keratitis, iritis, anterior chamber inflammation, blepharitis, photophobia, abnormal sensation in eye, keratoconjunctivitis sicca, conjunctivitis, allergic conjunctivitis, meibomianitis, eyelid margin crusting, eyelids pruritus, asthenopia, increased lacrimation, iris hyperpigmentation, growth of eye lashes, dark circles under eyes, reduced visual acuity, eye swelling, erythema of eyelid, eye allergy, conjunctival oedema, eyelid oedema, corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis.
	Frequency unknown	Macular oedema, eyelid ptosis, deepened lid sulcus, corneal disorder.
Cardiac disorders	Less Frequent	Bradycardia, arrhythmia, irregular heart rate.
	Frequency unknown	Cardiac failure, tachycardia, chest pain, palpitations.
Vascular disorders	Less Frequent	Hypotension, hypertension.
	Frequency unknown	Peripheral oedema.
Respiratory, thoracic and		
mediastinal disorders	Less Frequent	Dyspnoea, postnasal drip, dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort.
	Frequency unknown	Asthma.
Gastrointestinal disorders	Frequency unknown	Dysgeusia.
Hepatobiliary disorders	Less Frequent	Increased alanine aminotransferase, increased aspartate aminotransferase.
Skin and subcutaneous tissue disorders	Less Frequent	Skin discolouration, abnormal hair growth, contact dermatitis, hypertrichosis, skin hyperpigmentation (periocular), urticaria, alopecia.
	Frequency unknown	Rash.
Musculoskeletal and connective tissue disorders	Less Frequent	Pain in extremities.
Renal and urinary disorders	Less Frequent	Chromaturia.
General disorders and administration site conditions	Less Frequent	Fatigue, thirst.
Investigations	Less Frequent	Decreased heart rate.

* Adverse reactions observed with timolol.

d. 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 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
If overdosage with OPTURAN occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A.15.4 Ophthalmic Preparations, Other.
ATC Code: S01ED51.
OPTURAN contains two active components: travoprost and timolol maleate. These two components lower intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone. Travoprost is a prostaglandin selective F2α analogue agonist with an affinity for the prostaglandin FP receptor. It reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in man starts within approximately 2 hours after administration and maximum effect is reached after 12 hours. Low intraocular pressure can be maintained for periods exceeding 24 hours with a single dose. Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

5.2 Pharmacokinetic properties
Absorption
Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes ester hydrolysis in the cornea to the active free acid. Following once-daily administration in healthy participants (N = 22) for 5 days, travoprost free acid was not quantifiable in plasma samples from the majority of participants (94,4 %) and generally was not detectable one hour after dosing. When measurable (≥ 0,01 ng/ml, the assay limit of quantitation), concentrations ranged from 0,01 to 0,03 ng/ml. The mean timolol steady-state Cmax was 1,34 ng/ml and Tmax was approximately 0,69 hours after once-daily administration.

Distribution
Travoprost free acid can be measured in the aqueous humour during the first few hours in animals and in human plasma only during the first hour after ocular administration. Timolol can be measured in human aqueous humour after ocular administration of timolol and in plasma for up to 12 hours after ocular administration.

Biotransformation
Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin F2α which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β-oxidative cleavages of the upper side chain. Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring, and the other gives an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma t1/2 of timolol is 4 hours after ocular administration.

Elimination
Travoprost free acid and its metabolites are mainly excreted by the kidneys. Less than 2 % of an ocular dose of travoprost was recovered in urine as free acid. Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20 % of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Benzalkonium chloride
Macrogolglycerol hydroxystearate 40
Trometamol
Edetate disodium
Boric acid (E284)
Mannitol (E421)
Sodium hydroxide (for pH adjustment)
Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Unopened: 3 years.
After first opening: 28 days.

6.4 Special precautions for storage
Store at or below 25 ºC.
After first opening, the product does not require any special storage conditions.
Keep the container in the outer packaging in order to protect from light.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container
Polypropylene bottle of 5 ml with colourless LDPE nozzle and a white opaque HDPE/LDPE cap with tamper proof seal. Each bottle is enclosed in a sachet. Each bottle contains 2,5 ml solution.
Pack sizes: 1, 3, 4 or 6 bottles or multipack of 2 x 3 bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
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8 REGISTRATION NUMBER(S)
56/15.4/0782

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
10 June 2025

10 DATE OF REVISION OF THE TEXT
10 June 2025