PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

XOPTOLAT Ophthalmic Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre contains latanoprost 50 microgram (µg) and timolol maleate equivalent to timolol 5 mg.

Contains Zinc chloride 0,0025 % m/v as preservative.

Contains Boric acid 1,0 % m/v.

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Clear, colourless to light yellow viscous solution packed in a 5 ml coated natural LDPE sterile dropper bottle.

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.

4.2 Posology and Method of Administration

The tamper evident overcap should be removed before use.

Posology

Use in adults (including the elderly)

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

The dosage of **XOPTOLAT** should not exceed once daily since it has been reported that more frequent administration of latanoprost decreases the IOP lowering effect.

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

Paediatric population

Safety and effectiveness in children have not been established.

Method of administration

For ophthalmic use.

If more than one topical ophthalmic medicine is being used, they should be administered at least 5 minutes apart.

4.3 Contraindications

XOPTOLAT is contraindicated in patients with:

Known hypersensitivity to latanoprost, timolol maleate or any other component of XOPTOLAT listed in **Section 6.**

Reactive airway disease including bronchial asthma or a history of bronchial asthma, chronic obstructive pulmonary disease.

Sinus bradycardia, second or third degree atrioventricular block, cardiac failure, cardiogenic shock.

Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

Timolol

Systemic effects

XOPTOLAT is absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen

with systemic beta-adrenergic blocking-medicines may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

Cardiac disorders

Patients with a history of severe cardiac disease (e.g. coronary heart disease, sick sinus syndrome, Prinzmetal's angina, cardiac failure) should be monitored closely for signs of cardiac failure. The following cardiac reactions may occur after topical application of timolol maleate as in XOPTOLAT:

Aggravation of Prinzmetal's angina;

Hypotension;

Cardiac failure resulting in death;

Bradycardia

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

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation should be gradual and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.

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.

Aggravation of peripheral and central circulatory disorders may occur with application of **XOPTOLAT**.

Respiratory disorders

Bronchoconstriction and severe respiratory reactions, including fatal bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases. **XOPTOLAT** should be used with caution in these patients.

Hypoglycaemia / diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile insulin-dependent diabetes, as beta-blockers may increase the hypoglycaemic effect of medicines used to treat diabetes and may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of therapy may precipitate a worsening of this condition.

Corneal diseases

Close monitoring is required with frequent or prolonged use of **XOPTOLAT** in dry eye patients, or in conditions where the cornea is compromised.

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).

Anaphylactic reactions

When treated with beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

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

Surgical Anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. 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.

The anaesthesiologist should be informed when the patient is receiving timolol.

Concomitant therapy

Timolol may interact with other medicines e.g. hypoglycaemic medicines, phenothiazine and various anti- dysrhythmic medicines. Such interactions can have life-threatening consequences (see **section 4.5)**

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

Latanoprost

Other prostaglandin analogues

The concomitant use of two or more local prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended (see section 4.5).

Iris pigmentation changes

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. This effect has predominantly been seen in patients with mixed

coloured irises that contain the colour brown at baseline i.e. green-brown, yellow-brown or blue/grey-brown, and 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 in affected eyes, but the entire iris or parts of it may become more brownish. In patients with homogeneously blue, grey, green or brown eyes, the change has only rarely been seen.

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.

The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes.

No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent.

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.

Neither naevi nor freckles of the iris have been affected by the treatment.

Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed but patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia.

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.

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 latanoprost-timolol 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 should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues

Macular oedema

Macular oedema, including cystoid macular oedema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudo phakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema. XOPTOLAT should be used with caution in these patients.

Use of contact lenses

The contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

Boric acid warning

Do not give to a child less than 18 years old as this medicine contains boron and may impair fertility in the future.

Use in children

Safety and effectiveness in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies have not been performed with XOPTOLAT.

Beta-blockers

The effect on IOP or the known effects of systemic beta-blockade may be potentiated when latanoprost and timolol eye drops are given to patients already receiving an oral beta-adrenergic medicine and the use of two or more topical beta-adrenergic blocking medicines is not recommended (see **section 4.4**).

Prostaglandin analogues

There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended (see **section 4.4**).

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-dysrhythmics (including amiodarone and quinidine), digitalis glycosides, parasympathomimetics, guanethidine, narcotics and monoamine oxidase (MAO) inhibitors.

CYP2D6 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 (see **section 4.4**).

Adrenaline (Epinephrine)

Although latanoprost and timolol eye drops alone have little or no effect on pupil size, mydriasis has occasionally been reported when timolol is given with adrenalin (epinephrine).

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic medicines.

Beta-blockers can mask the signs and symptoms of hypoglycaemia (see **section 4.4**).

The concomitant use of latanoprost and timolol with hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines may have interactions with life-threatening consequences.

4.6 Fertility, pregnancy, and lactation

XOPTOLAT is contraindicated for use in pregnancy and breastfeeding (see section 4.3)

Pregnancy

Latanoprost

Reported studies in animals have shown reproductive toxicity (see **section 5.3**). The potential risk for humans is unknown.

Timolol

There are no adequate reported data for the use of timolol in pregnant women.

Timolol should not be used during pregnancy (see **section 4.3**).

Administration XOPTOLAT to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being hypotonic, collapsed and

hypoglycaemic. In addition, signs and symptoms of betablockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when betablockers have been administered until delivery.

Breastfeeding

XOPTOLAT should not be used in breastfeeding women, or breastfeeding should be stopped as timolol and Latanoprost and its metabolites may pass into breast milk (see **section 4.3**).

Fertility

Neither Latanoprost nor timolol have been reported to have any effect on male or female fertility in animal studies (see **section 5.3**).

4.7 Effects on ability to drive and use machines

Instillation of eye drops may cause transient blurring of vision. Patients can also experience dizziness visual impairment (see **section 4.8**) Until this has resolved, patients should not drive or use machines.

4.8 Undesirable Effects

Summary of the safety profile

Timolol is absorbed into the systemic circulation.

The most serious adverse reactions reported for Timolol are systemic beta blocking in nature, which include bradycardia, dysrhythmia, congestive heart failure, bronchospasm and allergic reactions. Incidence of systemic adverse drug reactions (ADRs) after topical ophthalmic administration is reported to be lower than for systemic administration

The adverse events of latanoprost and timolol eye drops are reported to be similar to those reported earlier for latanoprost and timolol (see **Section 4.4**). Based on evidence from consecutive photographs, increased iris pigmentation was reported in

16-20% of all patients who received latanoprost and timolol eye drops for up to one year.

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

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

The most frequently reported undesirable effects in reported clinical trials were irritation of the eye, including stinging, burning and itching, eye hyperaemia, corneal disorders, conjunctivitis, blepharitis, eye pain, headache and skin rash.

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

Tabulated summary of adverse events

Table 1: Adverse reactions reported in latanoprost-timolol trials

System Organ Class	Frequent	Less frequent
Infections and infestations	Infection, sinusitis, upper respiratory tract infection	
Metabolism and nutritional disorders	Diabetes mellitus, hypercholesterolaemia	
Psychiatric disorders	Depression	
Nervous system disorders	Headache	
Eye disorders	Eye irritation (including stinging, burning, itching, foreign body sensation), increased iris pigmentation, Abnormal vision, blepharitis, cataract, conjunctival disorder, conjunctivitis, corneal	Lacrimation increased

	disorder, errors of refraction, eye hyperaemia, eye pain, keratitis, photophobia, visual field defect.	
Vascular disorders	Hypertension	
Skin and subcutaneous tissue disorders	Hypertrichosis, rash, skin disorder	Pruritis
Musculoskeletal and connective tissue disorders	Arthritis	

Table 2: Adverse reactions reported for latanoprost

System Organ Class	**Frequent**	**Frequency not known**
Nervous system disorders		Dizziness
Eye disorders	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation), Eyelid oedema, transient punctate epithelial erosions	Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), vision blurred, iritis/uveitis, macular oedema including cystoid macular oedema, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation. Dry eye, trichiasis, iris cyst, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus, localised skin reaction on the eyelids, pseudopemphigoid of the ocular conjunctiva, darkening of the palpebral

		skin
Cardiac disorders		Angina, angina aggravation, dyspnoea, acute asthma attacks
Respiratory, thoracic and mediastinal disorders		Asthma, asthma aggravation, dyspnoea, acute asthma attacks
Skin and subcutaneous tissue disorders	Skin rash	Localised skin reaction on eyelids, darkening of palpebral skin of the eyelids
Musculoskeletal and connective tissue disorders		Muscle / joint pain
General disorders and administration site conditions		Non-specific chest pain

Table 3: Adverse reactions reported with timolol maleate (ocular administration)

System Organ Class	**Frequency not known**
Immune system disorders	Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localised and generalised rash, pruritus.
Metabolism and nutrition disorders	Anorexia, masked symptoms of hypoglycaemia in diabetic patients
Psychiatric disorders	Behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss, decreased libido, insomnia, nightmares, depression

Nervous system disorders	Dizziness, paraesthesia, somnolence, headache, cerebral ischaemia, cerebral vascular accident, increase in signs and symptoms of myasthenia gravis, syncope.
Eye disorders	Visual disturbance including refractive changes and diplopia, ptosis, cystoid macular oedema, decreased corneal sensitivity, choroidal detachment following filtration surgery, corneal erosion, keratitis, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing and redness), dry eyes, blepharitis, blurred vision
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Dysrhythmia, bradycardia, palpitation, cardiac arrest, heart block, worsening of angina pectoris, congestive heart failure, chest pain, oedema
Vascular disorders	Claudication, hypotension, cold hands and feet, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, bronchospasm (predominately in patients with pre-existing bronchospastic disease), nasal congestion, pulmonary oedema, respiratory failure
Gastrointestinal disorders	Diarrhoea, dry mouth, dyspepsia, nausea, retroperitoneal fibrosis, abdominal pain, vomiting, dysgeusia
Skin and subcutaneous tissue disorders	Alopecia, pseudopemphigoid, psoriasiform rash or exacerbation of psoriasis, skin rash
Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus, myalgia
Reproductive system and breast disorders	Impotence, Peyronie's disease, sexual dysfunction, decreased libido

General disorders and administration site conditions	Asthenia/fatigue

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No data have been reported in humans with regard to overdose with latanoprost and timolol.

Symptoms

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.

Treatment

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 µg 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 latanoprost and timolol eye drops 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 latanoprost and timolol resulting in systemic effects similar to those reported with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 15.4 Ophthalmological preparations, Other.

Ophthalmological-beta blocking agents - timolol, combinations

ATC code: S01ED51

Mechanism of action

XOPTOLAT consists of two components: latanoprost and timolol maleate. These two components decrease elevated IOP by different mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.

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 in man. 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 that has no significant intrinsic sympathomimetic, direct myocardial depressant or

membrane-stabilising activity. Timolol lowers IOP by decreasing aqueous humour formation in the ciliary epithelium.

The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable. Timolol has not been reported to significantly affect the permeability of the blood-aqueous barrier to plasma proteins. In rabbits, timolol was without effect on the regional ocular blood flow after chronic treatment.

Pharmacodynamic effects

Clinical efficacy and safety

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

5.2 Pharmacokinetic properties

Latanoprost

Absorption

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 reported to be well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Distribution

Reported studies in man indicate that the maximum concentration in the aqueous humour, approximately 30 ng/ml, is reached about 2 hours after topical administration of latanoprost alone. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctiva and the eye lids.

The acid of latanoprost has reported 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.

After topical ocular administration the systemic bioavailability of the acid of latanoprost is reported as 45%. The acid of latanoprost has reported a plasma protein binding of 87%.

Biotransformation and elimination

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 in reported animal studies and are excreted primarily in the urine.

Timolol

Absorption and distribution

The maximum concentration of timolol in the aqueous humour is reported to be 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 µg/day).

Biotransformation

The half-life of timolol in plasma is reported to be about 4 hours. Timolol is extensively metabolised in the liver.

Elimination

The metabolites are excreted in the urine together with some unchanged timolol.

Latanoprost and timolol

Pharmacokinetic/pharmacodynamic relationship

No pharmacokinetic interactions between latanoprost and timolol were reported, although there is a tendency for increased concentrations of the acid of latanoprost in

aqueous humour 1 to 4 hours after administration of latanoprost and timolol compared to monotherapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl methyl cellulose, Povidone (K-90), Zinc chloride, Polyethylene glycol 400, Boric acid, Tromethamine, Water For injection, Nitrogen

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months when stored at or below 25 ºC in the original carton.

6.4 Special precautions for storage

Store at or below 25 ºC in the original carton.

Do not refrigerate. Protect from light.

Once the bottle is opened the content must be used within 30 days and may be stored at or below 25 ºC. After opening the bottle must be stored in the carton to protect it from light.

Keep out of reach of children.

6.5 Nature and contents of container

Clear, colourless to light yellow viscous solution packed in a 5 ml coated natural LDPE sterile dropper bottle, plugged with 13 mm coated natural LDPE sterile plug and capped with 13 mm white, opaque HDPE pilfer proof sterile cap for dropper bottle.

6.6 Special precautions for disposal and other handling

None

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

52/15.4/0077

9. DATE OF FIRST AUTHORISATION

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