Professional Information for
TIMPROMAT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIMPROMAT eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains bimatoprost 0,3 mg and timolol maleate 6,8 mg equivalent to 5 mg timolol.

Excipients with known effect:

Benzalkonium chloride 0,005 % *w/v*.

Each ml contains 2,68 mg of dibasic sodium phosphate heptahydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

The solution is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are not sufficiently responsive to a topical beta-blocker or prostaglandin analogue given alone.

4.2 Posology and method of administration

Posology

Adults (including the elderly)

The recommended dose is one (1) drop of TIMPROMAT in the affected eye(s) once daily, administered in the morning or in the evening. It should be administered at the same time each day.

If a dose is missed, treatment should continue with the next dose as planned. The daily dose should not exceed one drop in the affected eye(s) daily.

Special populations

Renal and hepatic impairment

No data of use in patients with hepatic or renal impairment is available. Hence, caution should be used in treating such patients.

Paediatric population

The safety and efficacy of TIMPROMAT in children have not yet been established. No data are available. Its use is not recommended in children or adolescents.

Method of administration

For ophthalmic use.

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

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.

4.3 Contraindications

- Hypersensitivity to the active substances, bimatoprost and timolol or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block (not controlled with pace-maker), overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Systemic effects

The active substances (bimatoprost / timolol) in TIMPROMAT may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

Patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina, cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and therapy with other medicines should be considered. Patients with cardiovascular diseases should be monitored for signs of deterioration of these

diseases and of adverse reactions.

Patients with a history of severe cardiac disease should be monitored for signs of cardiac failure and their pulse rates should be monitored. Cardiac reactions, including, death in association with cardiac failures have been reported following administration of timolol maleate. Beta-blockers should only be given with caution to patients with first degree heart block due to its negative effect on conduction time.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorder (i.e. severe forms of Raynaud's disease or -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. TIMPROMAT should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Endocrine disorders

Beta-adrenergic blocking medicines may increase the hypoglycaemic effect of medicines used to treat diabetes, and can 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.

Corneal diseases

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

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 the 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-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 adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after

filtration procedures.

Surgical anaesthesia

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

Hepatic

Bimatoprost has no adverse reactions on liver function over 24 months in patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline. There are no known adverse reactions on liver function due to ophthalmic timolol administration.

Ocular

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin or periocular skin and increased iris pigmentation since these have been associated with bimatoprost and TIMPROMAT treatment. Some of these changes may be permanent and may result in differences in appearance between the eyes if only one eye is treated. After treatment discontinuation, pigmentation of iris may be permanent. After 12 months treatment, the incidence of iris pigmentation is 0,2 %.

After 12 months treatment with bimatoprost eye drops alone, the incidence is 1,5 % and does not increase following 3 years treatment.

	The pigmentation change is because of increased melanin content in the melanocytes rather than due to an increase in the number of melanocytes. The long-term effects of increased iridial pigmentation are not known. Iris colour changes seen with ophthalmic bimatoprost administration may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients. Macular oedema, including cystoid macular oedema, has been reported. Therefore, TIMPROMAT should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, and in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy). The use of bimatoprost in combination with timolol has not been studied in patients with inflammatory ocular conditions; neovascular, inflammatory, angle-closure glaucoma; congenital glaucoma or narrow angle glaucoma. TIMPROMAT should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated. In studies of bimatoprost 0,3 mg/ml in patients with glaucoma or ocular hypertension, it has been reported that more frequent exposure of the eye to more than one dose of bimatoprost daily may	

decrease the IOP-lowering effect. Patients using TIMPROMAT with other prostaglandin analogues should be monitored for intraocular pressure changes.

Skin

It is probable for hair growth to occur in areas where TIMPROMAT solution repeatedly comes into contact with the skin surface. Thus, it is important to apply TIMPROMAT as instructed and to avoid contact with the cheek or other skin areas.

Preservative - Benzalkonium chloride

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 medication over an extended period in patients with extensive ocular surface disease.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore, monitoring is required with frequent or prolonged use of TIMPROMAT in dry eye patients or where the cornea is compromised.

Contact lenses

TIMPROMAT contains benzalkonium chloride as a preservative, which may cause eye irritation and be absorbed by soft contact lenses. Contact lenses must be removed prior to instillation of TIMPROMAT and may be reinserted 15 minutes following administration. Furthermore, benzalkonium chloride is known to discolour soft contact lenses and contact with soft contact lenses must be avoided.

Paediatric population

Safety and effectiveness in children have not been established.

4.5 Interactions with other medicines and other forms of interaction

No specific interaction studies have been performed with the bimatoprost / timolol fixed combination.

Patients who are receiving a systemic (e.g. oral or intravenous) beta-adrenergic blocking medicine and TIMPROMAT should be observed for potential additive effects of beta-blockage, both systemic and on intraocular pressure.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when timolol containing eye drops are administered concomitantly with oral calcium channel blockers or beta-blockers, guanethidine, anti-dysrhythmics (including amiodarone), digoxin or parasympathomimetics and other anti-hypertensives.

Potentiated systemic beta-blockade (e.g. decreased heart rate,

depression) has been reported during concurrent treatment of CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) with timolol.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic medicines. Beta-blockers can mask the signs and symptoms of hypoglycaemia.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no adequate data from the use of the bimatoprost / timolol fixed combination in pregnant women.

Bimatoprost

No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses.

Timolol

Epidemiological studies have not revealed malformative effects but shown a risk for intra-uterine growth retardation when beta-blockers are administered by the oral route. Signs and symptoms of beta-

blockade including bradycardia, hypotension, respiratory distress and hypoglycaemia, have been observed in the neonate when beta-blockers have been administered until delivery. If TIMPROMAT is administered until delivery, the neonate should be closely monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice.

Breastfeeding

Timolol

Timolol is excreted in breast milk.

Bimatoprost

It is unknown if bimatoprost is excreted in human breast milk.

TIMPROMAT should not be used by breastfeeding women.

Fertility

There are no data on the effects of TIMPROMAT on human fertility.

4.7 Effects on ability to drive and use machines

TIMPROMAT has negligible influence on the ability to drive and use machines. If transient blurred vision occurs following administration, the patient should be advised to wait until the vision clears before driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Most adverse reactions are ocular in nature, mild in severity and not

serious. The most commonly reported side effect is conjunctival hyperaemia.

b. Tabulated summary of adverse reactions

Table 1: Bimatoprost / Timolol as in TIMPROMAT

System Organ Class	Frequency	Adverse Event
Immune system disorders	Frequency unknown	Hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy.
Psychiatric disorders	Frequency unknown	Insomnia, nightmare.
Nervous system disorders	Frequent	Headache.
	Frequency unknown	Dysgeusia, dizziness.
Eye disorders	Frequent	Conjunctival hyperaemia, growth of eyelashes, superficial punctuate keratitis, corneal erosion, burning sensation, eye pruritus, stinging sensation in the eye, foreign body sensation, eye dryness, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, conjunctival

			irritation, visual acuity worsened, blepharitis, eyelid oedema, eye irritation, lacrimation increased.
		Less frequent	Iritis, conjunctival oedema, eyelid pain, epiphora, asthenopia, trichiasis, abnormal sensation of the eye, iris hyperpigmentation, periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos, lagophthalmos, eyelid retraction, eyelash discolouration (darkening).
		Frequency unknown	Cystoid macular oedema, eye swelling, blurred vision, ocular discomfort.
	Cardiac disorders	Frequency unknown	Bradycardia.
	Vascular disorders	Frequency unknown	Hypertension.
	Respiratory, thoracic and mediastinal	Frequent	Rhinitis.
		Less frequent	Dyspnoea.
		Frequency	Bronchospasm

disorders	unknown	(predominantly in patients with pre-existing bronchospastic disease), asthma.
Skin and subcutaneous tissue disorders	Frequent	Blepharal pigmentation, hirsutism, skin hyperpigmentation (periocular).
	Frequency unknown	Alopecia, skin discolouration (periocular).
General disorders and administration site conditions	Frequency unknown	Fatigue.

Additional side effects that have been seen with either of the active substances (bimatoprost or timolol) and may potentially occur also with TIMPROMAT are listed below in Table 2:

Table 2

System Organ Class	Frequency	Adverse Event
Immune system disorders	Frequency unknown	Systemic allergic reactions including anaphylaxis.[1]
Metabolism and nutrition disorders	Frequency unknown	Hypoglycaemia.[1]
Psychiatric disorders	Frequency unknown	Depression[1], memory loss[1], hallucination[1].
Nervous system	Frequency	Syncope[1],

disorders	unknown	cerebrovascular accident[1], increase in signs and symptoms of myasthenia gravis[1], paraesthesia[1], cerebral ischaemia[1].
Eye disorders	Frequency unknown	Decreased corneal sensitivity[1], diplopia[1], ptosis[1], choroidal detachment (following filtration surgery (see section 4.4))[1], refractive changes (due to withdrawal of miotic therapy in some cases)[1], keratitis[1], allergic conjunctivitis[2], cataract[2], blepharospasm[2], retinal haemorrhage[2], uveitis.[2]
Ear and labyrinth disorders	Frequency unknown	Tinnitus. [1]
Cardiac disorders	Frequency unknown	Atrioventricular block[1], cardiac arrest[1], dysrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1], pulmonary oedema[1], worsening of angina

		pectoris[1].
Vascular disorders	Frequency unknown	Hypotension[1], claudication[1], Raynaud's phenomenon[1], cold hands and feet[1].
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Asthma exacerbation[2], COPD exacerbation[2], cough[1], nasal congestion[1], respiratory failure[1], upper respiratory infection[1].
Gastrointestinal Disorders	Frequency unknown	Nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], vomiting[1], anorexia[1].
Skin and subcutaneous tissue disorders	Frequency unknown	Psoriasiform rash[1] or exacerbation of psoriasis[1], skin rash[1], abnormal hair growth[2].
Musculoskeletal and connective tissue disorders	Frequency unknown	Myalgia[1], systemic lupus erythematosus[1].
Reproductive system and breast disorders	Frequency unknown	Decreased libido[1], sexual dysfunction[1], Peyronie's disease[1], retroperitoneal fibrosis[1].
General disorders and administration of site conditions	Frequency unknown	Asthenia[1, 2], peripheral oedema[2].

Investigations	Frequency unknown	Abnormal liver function tests (LFT)[1, 2]
Infections and infestations	Frequency unknown	Infection (primarily colds and upper respiratory symptoms)[2].

[1] adverse reactions observed with timolol

[2] adverse reactions observed with bimatoprost

c. Description of selected adverse reactions

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported rarely 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

4.9 Overdose

No cases of overdose have been reported, and it is unlikely to occur following ocular administration or to be associated with toxicity. Symptoms of systemic timolol overdose include bradycardia,

hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. Timolol does not readily dialyse.

If TIMPROMAT is accidentally ingested, the following information may be of use: in two-week oral rat and mouse studies, doses up to 100 mg/kg/day of bimatoprost did not produce toxicity. This dose is at least 70-times higher than the accidental dose of one bottle of TIMPROMAT in a 10 kg child.

In the event of overdose, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 15.4 Ophthalmic preparations – Others.

Pharmacotherapeutic group: Ophthalmological – beta-blocking agents – ATC code: S01ED51

Mechanism of action

Bimatoprost and timolol maleate, the two active substances, decrease elevated intraocular pressure (IOP) by complementary mechanisms of action. The combined effect results in additional IOP reduction compared to either medicine administered alone. The onset of action is rapid.

Bimatoprost is a potent ocular hypotensive medicine. It is a synthetic prostamide that is structurally related to prostaglandin F_{2a} (PGF_{2a}) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of biosynthesised

substances known as prostamides. However, the prostamide receptor has not yet been structurally identified. Bimatoprost reduces intraocular pressure by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor medicine that lowers IOP by reducing aqueous humour formation. The exact mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is possible. Timolol does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity.

Clinical effects

The IOP-lowering effect of TIMPROMAT is non-inferior to that achieved by combination treatment of bimatoprost (once daily) and timolol (twice daily), as single component medicines.

Data suggests that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

Paediatric population

The safety and efficacy in children aged 0 to 18 years has not been established.

5.2 Pharmacokinetic properties

Pharmacokinetics of TIMPROMAT

Systemic absorption of the individual components is minimal and not affected by co-administration in a single formulation. No accumulation occurs with either medicines.

Bimatoprost

Bimatoprost penetrates the human cornea and sclera well in vitro. Following ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0,03 % bimatoprost to both eyes for two weeks, blood concentrations peaks within 10 minutes after dosing and declines to below the lower limit of detection (0,025 ng/ml) within 1,5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hrs}$ values are similar on days 7 and 14 of treatment which indicates that a steady drug concentration is reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state is 0,67 l/kg. In human blood, bimatoprost resides mainly in the plasma and the plasma protein binding of bimatoprost is approximately 88 %.

Bimatoprost is the major circulating moiety in the blood once it reaches the systemic circulation following ocular dosing. Thereafter, bimatoprost undergoes oxidation, N-de-ethylation and glucuronidation to from a variety of metabolites.

Bimatoprost is primarily eliminated via renal excretion, with up to 67 % of an intravenous dose excreted in the urine, and 25 % of the

dose excreted via faeces. The elimination half-life after intravenous administration is approximately 45 minutes and the total blood clearance is 1,5 l/hr/kg.

Characteristics in elderly patients

After twice daily dosing, the mean $AUC_{0\text{-}24hrs}$ bimatoprost value in the elderly (subjects 65 years or older) is significantly higher than in young healthy adults. However, this is not clinically relevant as systemic exposure for both elderly and young subjects remain low following ocular dosing. There is no plasma accumulation of bimatoprost over time and the safety profile is similar in elderly and young patients.

Timolol

Following ocular administration of 0,5 % eye drop solution in humans undergoing cataract surgery, peak timolol concentration in the aqueous humour is reached one-hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is approximately 4 to 6 hours.

Timolol is partially metabolised by the liver with timolol and its metabolites excreted via the kidneys. Timolol is not extensively bound to plasma proteins.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Citric acid monohydrate

Dibasic sodium phosphate heptahydrate

Sodium chloride

Sodium hydroxide or hydrochloric acid

Purified water

6.2 Incompatibilities

Not applicable.

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 at or below 25 ºC. 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

A LDPE bottle with a white LDPE dropper insert, and closed with a dark blue, tamper-proof HDPE screw cap packed into a unit carton containing 1 bottle. Each LDPE bottle contains 2,5 ml or 3 ml 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

TRINITY PHARMA (PTY) LTD

106, 16th Road,

Midrand,

1686,

South Africa.

Telephone number: +27 (0) 12 664 1965 / +27 (0) 10 594 5610

Fax number: +27 (0) 12 664 2452

8. MARKETING AUTHORISATION NUMBER(S)

Timpromat: To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 April 2023

10. DATE OF REVISION OF THE TEXT

11 April 2023