

## Prescribing Information (Summary of Product Characteristics)

“Prescription only medicine”

### 1. Name of the Medicinal Product:

TIMATE (Timolol Eye Drops BP)

### 2. Qualitative and Quantitative Composition:

#### a) Qualitative

##### Composition Product

**Name:** TIMATE

**Generic Name:** Timolol Maleate BP

**Label Claim:** Each mL contains:

Timolol Maleate BP

Eq. to Timolol.....0.5% w/v

Benzalkonium Chloride Solution BP ..... 0.02% v/v

(As preservative)

Sterile Aqueous vehicle .....q.s.

#### b) Quantitative Composition

Each mL contains:

Timolol Maleate BP

Eq. to Timolol.....0.5% w/v

Benzalkonium Chloride Solution BP ..... 0.02% v/v

(As preservative)

Sterile Aqueous vehicle .....q.s.

For the full list of excipients, see section 6.1.

### 3. Pharmaceutical Form

Eye Drops

**Description:** Clear colourless solution.

### 4. Clinical Particulars

#### 4.1 Therapeutic indications

Timolol is a beta-adrenoceptor blocking agent used topically in the reduction of elevated intra-ocular pressure in various conditions including following:

- Patients with ocular hypertension;
- Patients with chronic open-angle glaucoma including aphakic patients
- Some patient with secondary glaucoma

#### 4.2 Posology and method of administration

##### Posology

Recommended therapy is one drop 0.5% solution in the affected eye twice a day.

Timolol may be used with other agent(s) for lowering intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended.

Intraocular pressure should be reassessed approximately four weeks after starting treatment because response to Timolol eye drops may

take a few weeks to stabilise.

Provided that the intra-ocular pressure is maintained at satisfactory levels, many patients can then be placed on once a day therapy.

#### Transfer from other agents

When another topical beta-blocking agent is being used, discontinue its use after a full day of therapy and start treatment with Timolol eye drops 0.5% the next day with one drop in each affected eye twice a day.

When transferring a patient from a single anti-glaucoma agent other than a topical beta-blocking agent, continue the agent and add one drop of Timolol eye drops 0.5% in each affected eye twice a day. On the following day, discontinue the previous agent completely, and continue with Timolol eye drops

#### Elderly

There has been wide experience with the use of timolol maleate in elderly patients. The dosage recommendations given above reflect the clinical data derived from this experience.

#### *Paediatric Population:*

Due to limited data, Timolol could only be recommended for use in primary congenital and primary juvenile glaucoma for a transitional period while decision is made on a surgical approach and in case of failed surgery while awaiting further options.

#### *Posology:*

Clinicians should strongly evaluate the risks and benefits when considering medical therapy with Timolol in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of Timolol.

No specific dosage recommendation can be given as there is only limited clinical data.

However, if benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If IOP could not be sufficiently controlled, a careful up titration to a maximum of two drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours should be preferred.

Furthermore, the patients, especially neonates, should be closely observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic side effects.

With regard to paediatric use, the 0.1% active agent concentration might already be sufficient.

#### *Duration of treatment:*

For a transient treatment in the paediatric population.

#### Method of 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.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled

improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to eye and subsequent loss of vision may result from using contaminated solutions.

#### **4.3 Contraindications**

- Cardiogenic shock
  - Overt cardiac failure
  - Second and third degree atrioventricular block not controlled with pace-maker
  - Sinus bradycardia, sick sinus syndrome sino-atrial block
  - Reactive airway disease including bronchial asthma or a history of bronchial asthma
  - Presence or history of severe chronic obstructive pulmonary disease
- Hypersensitivity to the active substance or to any of the excipients.

#### **4.4 Special warnings and precautions for use**

Like other topically applied ophthalmic drugs, timolol is absorbed systemically. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

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

Cardiac failure should be adequately controlled before beginning therapy with Timolol eye drops. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates monitored.

#### *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.

Timolol eye drops 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.

#### *Hypoglycaemia/diabetes*

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

Beta-blockers may also mask the signs of hyperthyroidism.

#### *Corneal diseases*

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

#### *Other beta-blocking agents*

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 agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended.

There have been reports of skin rashes and/or dry eyes associated with the use of beta- adrenoreceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy involving beta-blockade should be gradual.

#### *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 epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving timolol.

Timolol eye drops have been generally well tolerated in glaucoma patients wearing conventional hard contact lenses. Timolol eye drops have not been

studied in patients wearing lenses made with material other than polymethylmethacrylate (PMMA), which is used to make hard contact lenses. Timolol eye drops solution contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses; therefore, Timolol eye drops should not be used while wearing these lenses. The lenses should be removed before instillation of the drops and not reinserted earlier than 15 minutes after use.

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.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol has little or no effect on the pupil. When Timolol eye drops are used to reduce elevated intra-ocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multi-dose container.

There have been reports of bacterial keratitis associated with the use of multi dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

#### *Anaphylactic reactions*

While taking beta-blockers, patients with 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, may be unresponsive to the usual dose of epinephrine (adrenaline) used to treat anaphylactic reactions.

#### Paediatric Population:

Timolol solutions should generally be used cautiously in young glaucoma patients.

It is important to notify the parents of potential side effects so they can immediately discontinue the drug therapy. Signs to look for are, for example, coughing and wheezing.

Because of the possibility of apnoea and Cheyne-Stokes breathing, the drug should be used with extreme caution in neonates, infants and younger children. A portable apnoea monitor may also be helpful for neonates on Timolol.

## **4.5 Interaction with other medicinal product and other forms of interaction**

No specific drug interaction studies have been performed with timolol

maleate.

There is a potential for additive effects resulting in hypotension and/or marked

bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, rauwolfiaalkaloids, parasympathomimetics, guanethidine.

Although Timolol alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and epinephrine (adrenaline) has been reported occasionally.

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.

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Oral calcium-channel antagonists may be used in combination with beta- adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

The potential exists for hypotension, AV conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium-channel blocker is added to the treatment regimen. The nature of any cardiovascular adverse effects tends to depend on the type of calcium- channel blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker.

Intravenous calcium channel blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

#### **4.6 Fertility, Pregnancy and Lactation**

##### *Pregnancy*

There are no adequate data for the use of timolol maleate in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and

hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Timolol Eye Drops is administered until delivery, the neonate should be carefully monitored during the first days of life.

*Breast-feeding*

Timolol is detectable in human milk. A decision for breastfeeding mothers, either to stop taking Timolol or stop nursing, should be based on the importance of the drug to the mother.

**4.7 Effects on ability to drive and use machines**

Timolol has possible side effects such as dizziness, visual disturbances, refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and fatigue may affect some patients' ability to drive or operate machinery.

**4.8 Undesirable effects**

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. The following adverse reactions have been reported with *ocular* administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed. Additional side effects have been reported in clinical experiences with *systemic* timolol maleate, and may be considered potential effects of ophthalmic timolol maleate. Also listed are adverse reactions seen within the class of ophthalmic beta-blockers and may potentially occur with Timolol.

<i>Eye disorders:</i>	
<i>Ocular;</i>	Signs and symptoms of ocular irritation, (e.g. burning, stinging, itching, tearing, redness), conjunctivitis, blepharitis, keratitis, dryeyes, decreased corneal sensitivity, blurred vision, corneal erosion. Visual disturbance, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, and choroidal detachment following filtration surgery, 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
<i>Ear and labyrinth disorders</i>	
<i>ocular:</i>	tinnitus.
<i>Cardiac disorders:</i>	
<i>Ocular :</i>	Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure.

<i>Systemic:</i>	Atrioventricular block (second- or third-degree), sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation.
<i>Vascular disorders:</i>	



<i>Ocular;</i>	Hypotension, Raynaud's phenomenon, cold hands and feet, intermittent claudication.
<i>Respiratory, thoracic, and mediastinal disorders:</i>	
<i>Ocular:</i>	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough, respiratory failure.
<i>Systemic:</i>	rales.
<i>General disorders and administration site conditions:</i>	
<i>Ocular:</i>	Asthenia, fatigue.
<i>Systemic :</i>	Extremity pain, decreased exercise tolerance.
<i>Gastrointestinal disorders:</i>	
<i>Ocular:</i>	Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.
<i>Skin and subcutaneous tissue disorders:</i>	
<i>Ocular:</i>	Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.
<i>Systemic:</i>	Sweating, exfoliative dermatitis.
<i>Immune system disorders</i>	
<i>Ocular:</i>	Systemic lupus erythematosus, pruritus.
<i>Systemic:</i>	Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash, anaphylactic reaction.
<i>Psychiatric disorders</i>	
<i>Ocular:</i>	Depression, insomnia, nightmares, memory loss, Hallucination.
<i>Systemic:</i>	Diminished concentration, increased dreaming.
<i>Nervous system disorders</i>	
<i>Ocular:</i>	Syncope, cerebrovascular accident, cerebral ischemia, headache, dizziness, increase in signs and symptoms of myasthenia gravis, paraesthesia.
<i>Systemic:</i>	Vertigo, local weakness.
<i>Reproductive system and breast disorders:</i>	
<i>Ocular;</i>	Sexual dysfunction such as impotence, decreased libido. Peyronie's disease.
<i>Systemic :</i>	Micturition difficulties.
<i>Metabolism and nutrition disorders</i>	
<i>Ocular:</i>	Hypoglycaemia.
<i>Systemic:</i>	Hyperglycaemia.
<i>Musculoskeletal and connective tissue disorders:</i>	
<i>Ocular:</i>	Myalgia.

Systemic:	Arthralgia.
<i>Blood and lymphatic system disorders</i>	
Systemic:	Non-thrombocytopenic purpura.

## 4.9 Overdose

### *Symptoms*

There have been reports of inadvertent overdosage with Timolol eye drops resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and cardiac arrest.

### *Management*

If overdosage occurs, the following measures should be considered:

- 1 Gastric lavage, if ingested. Studies have shown that timolol does not dialyse readily.
- 2 Symptomatic bradycardia: Atropine sulphate, 0.25 to 2mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.
- 3 Hypotension: A sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.
- 4 Bronchospasm: Isoprenaline hydrochloride should be used. Additional therapy with aminophylline may be considered.
- 5 Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases, the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon which has been reported to be useful.
- 6 Heart block (second or third degree): Isoprenaline hydrochloride or a pacemaker should be used.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Ophthalmologicals, antiglaucoma preparations and miotics, beta-blocking agents,

ATC code: S01ED01.

### Mechanism of action

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic activity. Timolol maleate combines reversibly with the beta-adrenergic receptor, and this inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic stimulating (agonist) activity, whether these originate

from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist which will restore the usual biological response.

#### Clinical efficacy and safety

Unlike miotics, Timolol eye drops reduces IOP with little or no effect on accommodation or pupil size. In patients with cataracts, the inability to see around lenticular opacities when the pupil is constricted is avoided. When changing patients from miotics to Timolol eye drops a refraction might be necessary when the effects of the miotic have passed.

Diminished response after prolonged therapy with Timolol eye drops has been reported in some patients.

#### Paediatric Population:

There is only very limited data available on the use of Timolol (0.25%, 0.5% twice daily one drop) in the paediatric population. In one small, double blinded, randomized, published clinical study conducted for a treatment period up to 12 weeks on 105 children (n=71 on Timolol) aged 12 days – 5 years show to some extent evidence, that Timolol in the indication *primary congenital and primary juvenile glaucoma* is effective in short term treatment.

### **5.2 Pharmacokinetic Properties**

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

#### Paediatric Population:

As already confirmed by adult data, 80% of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva, nasolacrimal duct, oropharynx and gut, or the skin from tear overflow.

Due to the fact that the blood volume in children is smaller than that in adults a higher circulation concentration has to be taken into account. In addition, neonates have immature metabolic enzyme pathways and it may result in an increase in elimination half-life and potentiating adverse events.

Limited data show that plasma timolol levels in children after 0.25% greatly exceed those in adults after 0.5%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia.

### **5.3 Preclinical safety data**

No adverse ocular effects were observed in rabbits and dogs administered Timolol topically in studies lasting one and two years, respectively. The oral LD50 of the drug is 1,190 and 900 mg/kg in female mice and female rats, respectively.

*Carcinogenesis, mutagenesis, impairment of fertility*

In a two-year oral study of timolol maleate in rats there was a statistically significant ( $p \leq 0.05$ ) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (300 times the maximum recommended human oral dose). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose.

In a lifetime oral study in mice, there were statistically significant ( $p \leq 0.05$ ) increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day (500 times the maximum recommended human dose), but not at 5 or 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when evaluated in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mcg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant ( $p \leq 0.05$ ) elevations of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose-response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

## **6.0 Pharmaceutical particulars**

### **6.1 List of Excipients**

Disodium Hydrogen Ortho Phosphate BP, Sodium Chloride BP, Sodium Dihydrogen Ortho Phosphate BP, Disodium Edetate BP, Benzalkonium Chloride Solution BP, Sodium Hydroxide BP, Water for Injections BP.

**6.2 Incompatibilities**

None known.

**6.3 Shelf life**

24 months from the date of manufacturing.

Shelf Life after first opening: 1 Month

**6.4 Special precautions for storage**

Do not store above 30°C, keep in the outer carton to protect from light.

Do not refrigerate or freeze.

**6.5 Nature and contents of container**

White translucent LDPE Plastic granules bottles with White/Pink/Green or Blue colour spike cap pack size 1x5ml.

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

Any unused portion of this medicine or waste resulting from the use of this medicine should be disposed as per local regulatory requirement.

Tighten the cap on the nozzle as shown.

The spike in the cap will pierce the tip of the vial. Dispense drops with gentle pressure.

Replace the cap after every use. Not for Injection

For External Use Only Shake Well Before Use

Use the solution within one month after opening the vial.

**7. Marketing Authorization Holder**

Axa Parenterals

Limited Plot No 936,

937 & 939

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**8. Marketing Authorization Number**

TAN 22 HM 0006

**9. Date of renewal of the authorization**

Not Applicable

**10. Date of revision of the text**

April, 2022