PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TIMOPTOL-XE® 0,25 %

TIMOPTOL-XE® 0,50 %

Strength

TIMOPTOL-XE® 0,25 %: Each ml contains 2,5 mg timolol base

TIMOPTOL-XE® 0,50 %: Each ml contains 5,0 mg timolol base

Pharmaceutical form

Sterile Ophthalmic Gellan Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Timolol base

Quantitative declaration

TIMOPTOL-XE® 0,25 %: Each ml contains 2,5 mg timolol base (equivalent to 3,4 mg timolol maleate).

TIMOPTOL-XE® 0,50 %: Each ml contains 5,0 mg timolol base (equivalent to 6,8 mg timolol maleate).

Benzododecinium bromide as preservative 0,012 % *m/v* and 0,6 % *m/v* gellan gum.

3. PHARMACEUTICAL FORM

Sterile Ophthalmic Gellan Solution

Sterile, colourless to nearly colourless, slightly opalescent, slightly viscous, aqueous ophthalmic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIMOPTOL-XE® is indicated for the reduction of elevated intraocular pressure in patients with:

- ocular hypertension
- chronic open-angle glaucoma
- aphakia and glaucoma
- secondary glaucoma (some cases)
- narrow angles and a history of spontaneous or iatrogenically induced narrow-angle closure in the opposite eye in whom reduction of intraocular pressure is necessary (see section 4.4)

4.2 Posology and method of administration

Posology

The usual starting dose is one drop of 0,25 % TIMOPTOL-XE® in the affected eye(s) once a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0,5 % TIMOPTOL-XE® in the affected eye(s) once a day.

If needed, concomitant therapy with other agents for lowering intraocular pressure may be given with TIMOPTOL-XE®. The use of two topical beta-adrenergic blockers is not recommended (see section 4.4).

Other topically applied medications should be administered no less than 10 minutes before TIMOPTOL-XE®.

How to Transfer Patients from Other Therapy

When a patient is transferred from TIMOPTOL® to TIMOPTOL-XE®, TIMOPTOL® should be discontinued after proper dosing on one day, and treatment with the same concentration of TIMOPTOL-XE® started on the following day.

When a patient is transferred from another topical ophthalmic beta-adrenergic blocker, that medicine should be discontinued after proper dosing on one day and treatment with TIMOPTOL-XE® started on the following day with 1 drop of 0,25 % TIMOPTOL-XE® in the affected eye once a day. The dose may be increased to one drop of 0,5 % TIMOPTOL-XE® once a day if the clinical response is not adequate.

When a patient is transferred from a single anti-glaucoma agent, other than a topical ophthalmic beta-adrenergic blocker, continue the medicine and add one drop of 0,25 % TIMOPTOL-XE® to each affected eye once a day. On the following day, discontinue the previously used anti-glaucoma medicine and continue TIMOPTOL-XE®. If a greater response is required, substitute one drop of 0,5 % TIMOPTOL-XE® for the 0,25 dosage.

When changing patients from miotics to TIMOPTOL-XE®, refraction may be necessary after the effects of the miotic have passed.

Method of administration

Invert the closed container and shake once before each use. It is not necessary to shake the container more than once. When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption may be reduced. This may result in an increase in local activity.

4.3 Contraindications

TIMOPTOL-XE® is contraindicated in patients with:

- Reactive airway disease, including bronchial asthma or a history of bronchial asthma, or chronic obstructive pulmonary disease
- Sinus bradycardia, heart block, including sino-atrial block, sick sinus syndrome sino-atrial block, second or third degree atrioventricular block, not controlled with pace-maker, overt cardiac failure, uncontrolled cardiac failure; cardiogenic shock

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Concomitant use with calcium-channel antagonists in patients with impaired cardiac function
- Advanced peripheral arterial insufficiency
- Raynaud's syndrome

Timoptol-XE® should not be used in patients wearing contact lenses as it has not been studied in these patients.

4.4 Special warnings and precautions for use

TIMOPTOL-XE® is absorbed systemically and the same types of cardiovascular, pulmonary and other adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration.

Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2. Prolonged use may be followed with a decreased response.

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. Cardiac complications, including death in association with cardiac failure, have been reported following administration of beta-adrenergic blocking agents. Cardiac failure should be adequately controlled before beginning therapy with TIMOPTOL-XE®. In patients with a history of cardiac disease, signs of cardiac failure should be sought and pulse rates should be monitored. Due to its negative effect on conduction time, TIMOPTOL-XE® should not be given to patients with first degree heart block.

Respiratory disorders

Respiratory complications, including death due to bronchospasm in patients with asthma have been reported following administration of beta-adrenergic blocking agents. These are potential complications of therapy with TIMOPTOL-XE®.

Vascular disorders

Patients with peripheral arterial insufficiency or circulatory disturbance/disorders (e.g. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution (see section 4.3).

Hypoglycaemia/diabetes

TIMOPTOL-XE® should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. TIMOPTOL-XE® may mask the signs and symptoms of acute hypoglycaemia and the body's response to hypoglycaemia.

Masking of hyperthyroidism

TIMOPTOL-XE® may mask certain clinical signs of hyperthyroidism (e.g. tachycardia). Patients suspected of developing hyperthyroidism should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, such as TIMOPTOL-XE®, which might precipitate a thyroid storm (see section 4.3).

Corneal diseases

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

Other beta-blocking agents

Patients who are already receiving an oral beta-adrenergic blocking medicine(s) and who are given TIMOPTOL-XE® should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

The use of TIMOPTOL-XE® plus another topical beta-adrenergic blocking medicine is not recommended (see section 4.5).

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

In patients with angle-closure glaucoma, the immediate objective of treatment is to re-open the angle. This requires constricting the pupil with a miotic. Timolol maleate has little or no effect on the pupil. Should TIMOPTOL-XE® be used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used together with a miotic and not on its own.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy such as TIMOPTOL-XE® after surgical and other filtration procedures.

TIMOPTOL-XE® has not been studied in patients wearing contact lenses (see section 4.3).

The dispenser of TIMOPTOL-XE® contains benzododecinium bromide as a preservative. In a clinical study, the time required to eliminate 50 % of the gellan solution from the eye was up to 30 minutes.

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.

The most frequent medicine related side effects are transient blurred vision, which may last from 30 seconds to 5 minutes and in rare cases up to 30 minutes or longer, following instillation. Blurred vision and potential visual disturbances may impair the ability to perform hazardous tasks such as operating machinery or driving a motor vehicle. Ensure that vision is clear before driving a motor vehicle or operating machinery.

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 multidose container (see section 4.2). There

have been reports of bacterial keratitis associated with the use of multiple 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 using TIMOPTOL-XE®, 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, whether accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

Paediatric population

Safety and efficacy of TIMOPTOL-XE® has not been established in children.

4.5 Interaction with other medicines and other forms of interaction

No specific medicine interaction studies have been performed with timolol.

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, rauwolfia alkaloids, parasympathomimetics, guanethidine.

Mydriasis resulting from concomitant therapy with epinephrine (adrenaline) has been reported. The potential for mydriasis exists from concomitant therapy with TIMOPTOL-XE® and epinephrine (adrenaline).

Close observation of the patient is recommended when TIMOPTOL-XE® is administered to patients receiving catecholamine-depleting medication such as rauwolfia derivatives or antidysrhythmics and parasympathomimetics, because of the possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Hypotension, atrioventricular (AV) conduction disturbances and left ventricular failure may occur in patients receiving TIMOPTOL-XE® when an oral calcium-channel blocker is added to the treatment regimen (see section 4.3). The nature of any cardiovascular adverse effect 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.

The concomitant use of TIMOPTOL-XE® and digoxin with a calcium antagonist (for example diltiazem or verapamil) may have additive effects in prolonging AV conduction time. 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. Intravenous calcium-channel blockers should be used with caution in patients receiving TIMOPTOL-XE®.

Oral beta-adrenergic blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. Therefore, if clonidine and TIMOPTOL-XE® are co-administered, TIMOPTOL-XE® should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta blocker therapy, the introduction of beta-adrenergic blocking agent should be delayed for several days after clonidine administration has stopped. Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, SSRIs including fluoxetine and paroxetine) and TIMOPTOL-XE®.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data for the use of timolol in pregnant women. TIMOPTOL-XE® should not be used during pregnancy.

To reduce the systemic absorption, see section 4.2.

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 TIMOPTOL-XE® is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breastfeeding

Timolol is secreted in human milk. Women on TIMOPTOL-XE® should not breastfeed their infants. A decision for breastfeeding mothers, either to stop taking TIMOPTOL-XE® or stop nursing, should be based on the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

Transient blurred vision following instillation may occur, generally lasting from 30 seconds to 5 minutes, and in rare cases, up to 30 minutes or longer. Blurred vision and potential visual disturbances, refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and fatigue may impair the ability to perform hazardous tasks such as operating machinery or driving a motor vehicle.

4.8 Undesirable effects

Like other topically applied ophthalmic medicines, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. The most frequent medicine-related complaint in clinical studies was transient blurred vision (6,0 %), lasting from 30 seconds to 5 minutes following instillation. Diminished responsiveness to TIMOPTOL-XE® after prolonged therapy has been reported.

The following adverse reactions have been reported with ocular administration of TIMOPTOL-XE®. Additional adverse reactions have been reported in clinical experiences with systemic timolol, and may be considered potential effects of ophthalmic timolol. Also listed are adverse reactions seen within the class of ophthalmic beta-blockers and may potentially occur with TIMOPTOL-XE®.

Very Common (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1 000 to <1/100)	**Rare** (≥ 1/10 000 to <1/1 000)	**Not known**
Blood and lymphatic system disorders *Systemic*				
				non-thrombocytopenic purpura
Immune system disorders *Ocular*				
			systemic lupus erythematosus, signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash	pruritis
Systemic				

Very Common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1 000 to <1/100)	Rare (≥ 1/10 000 to <1/1 000)	Not known
				anaphylactic reaction
Metabolism and nutrition disorders *Ocular*				
				hypoglycaemia
Systemic				
				hyperglycaemia, masking of the signs and symptoms of acute hypoglycaemia (see section 4.4)
Psychiatric disorders *Ocular*				
		depression	insomnia, nightmares, memory loss	hallucination
Systemic				
				impaired concentration, increased dreaming nightmares, and other psychiatric disturbances

Very Common (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1 000 to <1/100)	**Rare** (≥ 1/10 000 to <1/1 000)	**Not known**
				(e.g. anxiety and nervousness)
Nervous system disorders *Ocular*				
	headache	syncope, dizziness	cerebrovascular accident, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis, paraesthesia	
Systemic				
				vertigo, local weakness
Eye disorders *Ocular*				
transient blurred vision (lasting from 30 seconds to 5 minutes following instillation)	burning and stinging, conjunctival injection, discharge, foreign body sensation, and itching. Signs and symptoms of ocular irritation	visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases)	diplopia, ptosis, choroidal detachment following filtration surgery or other filtration procedures (see section 4.4)	corneal erosion

Very Common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1 000 to <1/100)	Rare (≥ 1/10 000 to <1/1 000)	Not known
	(e.g. burning, stinging, itching, tearing, redness) conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity, and dry eyes			
Ear and labyrinth disorders *Ocular*				
			tinnitus	
Cardiac disorders *Ocular*				
		bradycardia	dysrhythmia, heart block, congestive heart failure, palpitation, cardiac arrest, oedema, chest pain	atrioventricular block, cardiac failure
Systemic				
				AV block (2nd- or 3rd- degree), sino-atrial block,

Very Common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1 000 to <1/100)	Rare (≥ 1/10 000 to <1/1 000)	Not known
				pulmonary oedema, worsening of peripheral arterial insufficiency (including Raynaud's phenomenon, intermittent claudication), worsening of angina pectoris, vasodilation
Vascular disorders *Ocular*				
			hypotension, claudication, Raynaud's phenomenon, cold hands and feet	
Respiratory, thoracic, and mediastinal disorders *Ocular*				
		dyspnoea	bronchospasm (predominantly in patients with pre-existing	

Very Common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1 000 to <1/100)	Rare (≥ 1/10 000 to <1/1 000)	Not known
			bronchospastic disease such as asthma or COPD), respiratory failure, cough	
Systemic				
				rales
Gastrointestinal disorders *Ocular*				
		nausea, dyspepsia	diarrhoea, dry mouth	dysgeusia, abdominal pain, vomiting
Systemic				
				abdominal pain, vomiting
Skin and subcutaneous tissue disorders *Ocular*				
			alopecia, psoriasiform rash or exacerbation of psoriasis	skin rash
Systemic				
				sweating, exfoliative dermatitis
Musculoskeletal and connective tissue disorders				

Very Common (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1 000 to <1/100)	**Rare** (≥ 1/10 000 to <1/1 000)	**Not known**
Ocular				
				myalgia
Systemic				
				arthralgia, myalgia, extremity pain
Reproductive system and breast disorders *Ocular*				
			Peyronie's disease, decreased libido	sexual dysfunction such as impotence
Systemic				
				micturition difficulties, impotence
General disorders and administration site conditions *Ocular*				
	asthenia, fatigue			
Systemic				
				extremity pain, decreased exercise tolerance, local weakness
Investigations *Systemic*				

Very Common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1 000 to <1/100)	Rare (≥ 1/10 000 to <1/1 000)	Not known
				increases in blood urea, serum potassium, serum uric acid and triglycerides and decreases in haemoglobin, haematocrit and HDL-cholesterol

Post-marketing Experience

The following adverse effects have been reported but a causal relationship to therapy with TIMOPTOL-XE® has not been established.

Metabolism and nutrition disorders

Anorexia

Nervous system disorders

CNS effects (e.g. behavioural changes including confusion, hallucinations, disorientation and somnolence)

Eye disorders

Aphakic cystoid macular oedema

Cardiac and vascular disorders

Hypertension

Respiratory, thoracic and mediastinal disorders

Nasal congestion

Gastro-intestinal disorders

Retroperitoneal fibrosis

Skin and subcutaneous tissue disorders

Pseudopemphigoid

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 Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Alternatively report to the following e-mail address: ZADrugsafety@mundipharma.co.za.

4.9 Overdose

Overdosage with TIMOPTOL-XE® has resulted in systemic effects similar to those seen with systemic beta-adrenergic blockers e.g. dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (also see section 4.8).

The following specific therapeutic measures should be considered:

1. Symptomatic bradycardia: Administer atropine sulphate intravenously in a dosage of 0,25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be cautiously administered. In refractory cases the use of a transvenous cardiac pacemaker may be considered.
2. Heart block (second or third degree): Treatment is symptomatic and supportive.
3. Hypotension: Use sympathomimetic pressor medication therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride has been reported to be useful.
4. Acute cardiac failure: Conventional therapy with digoxin, 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 hydrochloride, which has been reported to be useful.

5. Bronchospasm: Additional therapy with aminophylline may be considered.

Timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 15.4 Ophthalmic Preparations, other.

ATC Code: S01ED01.

Mechanism of action

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent, which reduces intraocular pressure. This formulation (gellan solution) contains a purified anionic heteropolysaccharide derived from gellan gum. Aqueous solutions of the gellan gum form a clear transparent gel at low polymer concentrations in the presence of cations. When the timolol maleate sterile ophthalmic gellan solution contacts the precorneal tear film, it becomes a gel. Maximum reduction of intraocular pressure occurs in two to four hours with timolol. The effect of timolol in lowering intraocular pressure was evident for 24 hours with a single dose of timolol. However, these effects may be variable in individual patients. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established. A fluorescein study and tonography study in man suggests that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. Timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size.

5.2 Pharmacokinetic properties

Onset of action of timolol maleate usually occurs approximately 20 minutes after topical application to the eye.

5.3 Preclinical safety data

No adverse ocular effects were observed in monkeys and rabbits administered Timoptol-XE® topically in studies lasting 12 months and one month, respectively. The oral LD_{50} of timolol is 1190 and 900 mg/kg in female mice and female rats, respectively. The oral LD_{50} of gellan gum is greater than 5000 mg/kg in rats. 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 phaeochromocytomas 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 postmortem 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.

In oral studies of gellan gum administered to rats for up to 105 weeks at concentrations up to 5 % of their diet and to mice for 96-98 weeks at concentrations up to 3 % of their diet, no overt signs of toxicity and no increase in the incidence of tumours were observed. 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, 5000 or 10000 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. Gellan gum was devoid of mutagenic potential when evaluated *in vivo* (mouse) in micronucleus assay using doses up to 450 mg/kg. In addition, gellan gum in concentrations up to 20 mg/ml was not detectably mutagenic in the following in-vitro assays:
(1) unscheduled DNA synthesis in rat hepatocytes assay, (2) V-79 mammalian cell mutagenesis assay, and (3) chromosomal aberrations in Chinese hamster ovary cells assay. In Ames tests, gellan gum (in concentrations up to 1000 mcg/plate, which is its limit of solubility) did not induce a twofold or greater increase in revertants relative to the solvent control. It is therefore not detectably mutagenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients are: Gellan gum, mannitol, tromethamine, and water for injection. Benzododecinium bromide is added as a preservative.

6.2 Incompatibilities

None known

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ºC. Avoid freezing. Protect from light.

Do not use more than 30 days after opening.

6.5 Nature and contents of container

TIMOPTOL-XE® is supplied in an Ocumeter™ containing 2,5 ml solution.

TIMOPTOL-XE® 0,25 % is a sterile, colourless to nearly colourless, slightly opalescent, slightly viscous, aqueous ophthalmic solution. The label on the cap of the Ocumeter™ container is light blue.

TIMOPTOL-XE® 0,5 % is a sterile, colourless to nearly colourless, slightly opalescent, slightly viscous, aqueous ophthalmic solution. The label on the cap of the Ocumeter™ container is dark blue.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd

Block D, Grosvenor Square

Park Lane, Century City,

Cape Town

7441

South Africa

8. REGISTRATION NUMBER(S)

South Africa: S3

TIMOPTOL-XE® 0,25 %: 29/15.4/0230

TIMOPTOL-XE® 0,50 %: 29/15.4/0231

Namibia: NS2

TIMOPTOL-XE® 0,25 %: 13/15.4/0008

TIMOPTOL-XE® 0,50 %: 13/15.4/0009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 March 1996

10. DATE OF REVISION OF THE TEXT

11 March 2022