PRODUCT INFORMATION

TIMOPTOL-XE®
(timolol maleate, MSD)

Sterile Ophthalmic Gellan Solution

CHEMISTRY

Timolol maleate is a beta-adrenergic receptor blocking agent. The chemical name is (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (Z)-2-butenedioate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom and is provided as the levo isomer. The empirical formula is C_{13}H_{24}N_{4}O_{3}S.C_{4}H_{4}O_{4} and the structural formula is:

![Structural formula of timolol maleate](image)

Timolol maleate has a molecular weight of 432.50. It is a white, odourless, crystalline powder which is soluble in water, methanol, and alcohol.

DESCRIPTION

TIMOPTOL-XE® (timolol maleate, MSD) Sterile Ophthalmic Gellan Solution is a formulation of timolol maleate (TIMOPTOL) containing gellan gum.

Gellan gum is a highly purified anionic heteropolysaccharide. Aqueous solutions of gellan gum form a clear transparent gel at low polymer concentrations in the presence of cations. When TIMOPTOL-XE contacts the precorneal tear film, it becomes a gel. The concentration of sodium cation in tears is ideally suited to cause gelation of the material when topically instilled in the conjunctival sac.

Each mL of TIMOPTOL-XE 0.25% contains 2.5mg of timolol (3.4mg of timolol maleate). Each mL of TIMOPTOL-XE 0.5% contains 5.0mg of timolol (6.8mg of timolol maleate).

* Registered Trademark of Merck & Co., Inc., Whitehouse Station, N.J., U.S.A.
TIMOPTOL-XE also contains the following inactive ingredients: gellan gum, trometamol, mannitol and water for injection. Benzododecinium bromide 0.012% is added as the preservative.

**PHARMACOLOGY**

TIMOPTOL-XE reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Clinical studies have shown that the intraocular pressure lowering effect of TIMOPTOL-XE administered once a day is equivalent to TIMOPTOL administered twice a day. The vehicle of TIMOPTOL-XE, gellan gum, increases the contact time of the drug with the eye.

Maximum reduction of intraocular pressure occurs in two to four hours with TIMOPTOL-XE. Significant lowering of intraocular pressure has been maintained for 24 hours with both 0.25% and 0.5% TIMOPTOL-XE.

TIMOPTOL-XE has a safety profile similar to that of TIMOPTOL, and both are generally well tolerated. In the three studies comparing TIMOPTOL-XE 0.5% once a day to TIMOPTOL 0.5% twice a day, TIMOPTOL-XE did not reduce mean heart rate as much as TIMOPTOL (See PRECAUTIONS). At trough (24 hours post-dose TIMOPTOL-XE, 12 hours post-dose TIMOPTOL), the mean reduction was 0.8 beats/minute for TIMOPTOL-XE and 3.6 beats/minute for TIMOPTOL; whereas at two hours post-dose, the mean reduction in heart rate was comparable (3.8 beats/minute for TIMOPTOL-XE and 5 beats/minute for TIMOPTOL). There was a higher incidence of transient blurred vision following instillation in patients administered TIMOPTOL-XE.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established. A fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

In clinical studies timolol maleate was generally effective in more patients and produced fewer and less severe side effects than either pilocarpine or adrenaline.

Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon, and the dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided. When changing patients from miotics to TIMOPTOL-XE, refraction may be necessary after the effects of the miotic have passed.

As with other antiglaucoma drugs, diminished responsiveness to timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies of TIMOPTOL in which 164 patients were followed for at least 3 years, no significant difference in mean intraocular pressure was observed after initial stabilisation. This indicates that the intraocular pressure-lowering effect of timolol maleate is well maintained.
Timolol maleate is a nonselective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having 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 biologic response.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

**Pharmacokinetics**

Following 8 days of once daily application of 0.5% TIMOPTOL-XE in the eye, peak plasma concentrations of timolol averaged <0.3 ng/mL within 4 hours after the last dose. The maximum plasma levels measured approached 0.5 ng/mL at 1 to 2 hours following the last dose.

**INDICATIONS**

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

- ocular hypertension
- chronic open-angle glaucoma
- aphakia and glaucoma

**CONTRAINDICATIONS**

TIMOPTOL-XE is contraindicated in patients with:

- Bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock.
- Hypersensitivity to any component of this product.
PRECAUTIONS

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration (see ADVERSE REACTIONS/Potential Side Effects)

Cardiac failure should be adequately controlled before beginning therapy with TIMOPTOL-XE. In patients with a history of severe cardiac disease, signs of cardiac failure should be sought and pulse rates should be monitored.

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

Patients who are already receiving a beta-adrenergic blocking agent orally 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 two topical beta-adrenergic blocking agents is not recommended.

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 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 with a miotic and not alone.

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

TIMOPTOL-XE has not been studied in patients wearing contact lenses. In a clinical study, the time required to eliminate 50% of the gellan solution from the eye was up to 30 minutes.

Hypersensitivity to any of its ingredients, including the preservative, may develop. Contact irritancy due to the preservative may occur.

RISK FROM ANAPHYLACTIC REACTION

While taking 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, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.
USE IN PREGNANCY (Category C)

TIMOPTOL-XE has not been studied in human pregnancy. Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and newborn infant. During the latter stages of pregnancy and birth, these drugs should be given only after weighing the needs of the mother against the risk to the foetus.

USE IN LACTATION

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from TIMOPTOL-XE in infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

USE IN CHILDREN

Safety and efficacy in children have not been established by adequate and well controlled studies.

DRUG INTERACTIONS

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

The potential exists for hypotension, atrioventricular (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 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 beta-adrenergic blocking agents and digitalis with either 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 beta-adrenergic blocking agents.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine and SSRIs) and timolol.
Although timolol maleate used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with adrenaline has been reported occasionally. The potential for mydriasis exists from concomitant therapy with TIMOPTOL-XE and adrenaline.

β adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. Caution should be exercised in patients using these drugs concomitantly. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate."

**ADVERSE REACTIONS**

TIMOPTOL-XE is usually well tolerated. The most frequent drug-related complaint in the original clinical trials for TIMOPTOL-XE was transient blurred vision (6.0%), lasting from 30 seconds to 5 minutes, following instillation.

In clinical studies, the drug-related adverse experiences observed for TIMOPTOL-XE were similar to those of TIMOPTOL, with the exception of a higher incidence of transient blurred vision for TIMOPTOL-XE (6%) compared to TIMOPTOL (1.6%). Drug-related adverse experiences caused 3.4% of patients treated with TIMOPTOL-XE to discontinue compared to 1.4% of patients treated with TIMOPTOL. Less than 1% of patients discontinued TIMOPTOL-XE due to transient blurred vision.

The following possibly, probably, or definitely drug-related adverse reactions occurred with frequency of at least 1% in active treatment controlled clinical trials:

**Ocular**

*Common (≥1% and <10%)*
- Blurred vision, burning and stinging, conjunctival injection, discharge, foreign body sensation, itching.

The following additional 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. (also see Potential Side Effects).

**Special Senses**
- Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity and dry eyes. Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, choroidal detachment following filtration surgery (see PRECAUTIONS), tinnitus.

**Cardiovascular**
- Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest, oedema, claudication, Raynaud’s phenomenon, cold hands and feet.

**Respiratory**
- Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), exacerbation of asthma, respiratory failure, dyspnoea, cough.
Body as a Whole
   Headache, asthenia, fatigue, chest pain.

Integumentary
   Alopecia, psoriasiform rash or exacerbation of psoriasis.

Hypersensitivity
   Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash.

Nervous system/Psychiatric
   Dizziness, depression, insomnia, nightmares, memory loss, paraesthesia.

Neuromuscular
   Increase in signs and symptoms of myasthenia gravis.

Digestive
   Nausea, diarrhoea, dyspepsia, dry mouth.

Urogenital
   Decreased libido, Peyronie’s disease.

Immunologic
   Systemic lupus erythematosus.

Potential Side Effects

The following side effects have been reported in clinical experience with systemic timolol maleate and may be considered potential side effects of ophthalmic timolol maleate.

Body as a Whole
   extremity pain
   decreased exercise tolerance

Cardiovascular
   AV block (2nd or 3rd degree)
   sinoatrial block
   pulmonary oedema
   worsening of arterial insufficiency
   worsening of angina pectoris
   vasodilation

Digestive
   vomiting

Endocrine
   hyperglycaemia
   hypoglycaemia
Integumentary
    pruritus
    sweating
    exfoliative dermatitis

Musculoskeletal
    arthralgia

Nervous System
    vertigo
    local weakness

Psychiatric
    nervousness
    diminished concentration
    hallucinations
    increased dreaming
    somnolence

Haematologic
    nonthrombocytopenic purpura

Respiratory
    rales

Urogenital
    impotence
    micturition difficulties

Clinical Laboratory Test findings

Clinically important changes in standard laboratory parameters were rarely associated with
the administration of systemic timolol maleate. Slight increases in serum urea, serum
potassium, serum uric acid and triglycerides and slight decreases in haemoglobin,
haematocrit, and HDL-cholesterol occurred, but were not progressive or associated with
clinical manifestations.

Side-Effects, Causal Relationship Unknown

The following adverse effects have been reported but a causal relationship to therapy with
timolol maleate has not been established: aphakic cystoid macular oedema, nasal
congestion, anorexia, CNS effects (eg., behavioural changes including confusion, anxiety,
disorientation and other psychic disturbances), hypertension, retroperitoneal fibrosis, and
pseudopemphigoid.
DOSAGE AND ADMINISTRATION

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. Invert the container and shake once energetically before instillation. Depress the bottom of the bottle to dispense one drop.

Dosages higher than one drop of 0.5% TIMOPTOL-XE once a day have not been studied.

If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with TIMOPTOL-XE. Other topically applied medications should be administered no less than 10 minutes before TIMOPTOL-XE. The use of two topical beta-adrenergic blocking agents is not recommended (see PRECAUTIONS).

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 blocking agent, that agent 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 antiglaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent and add one drop of 0.25% TIMOPTOL-XE to each affected eye once a day. On the following day, discontinue the previously used antiglaucoma agent and continue TIMOPTOL-XE. If a greater response is required, substitute one drop of 0.5% TIMOPTOL-XE for the 0.25% dosage.

OVERDOSAGE

There have been reports of inadvertent overdosage with TIMOPTOL resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Contact the Poisons Information Centre for advice on management.

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 isoprenaline hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.
(2) Heart block (second or third degree): Administer isoprenaline hydrochloride or insert a transvenous cardiac pacemaker.

(3) Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or noradrenaline. In refractory cases the use of glucagon hydrochloride has been reported to be useful.

(4) 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 hydrochloride, which has been reported to be useful.

(5) Bronchospasm: Administer isoprenaline hydrochloride. Additional therapy with aminophylline may be considered.

Timolol does not dialyse readily.

PRESENTATION

TIMOPTOL-XE is a sterile, colourless to nearly colourless, slightly opalescent, slightly viscous, aqueous ophthalmic solution.

TIMOPTOL-XE 2.5 mg/mL : 2.5 mL bottle with a controlled dropper tip and white cap. Store at or below 25°C. Avoid freezing. Protect from light. Discard within 28 days of opening.

TIMOPTOL-XE 5.0 mg/mL : 2.5 mL bottle with a controlled dropper tip and white cap. Store at or below 25°C. Avoid freezing. Protect from light. Discard within 28 days of opening.

SPONSOR

Merck Sharp & Dohme (Australia) Pty. Limited
54-68 Ferndell St., South Granville 2142

This document was approved by the Therapeutic Goods Administration on 29 July 1999. Editorial Changes notified to the TGA on 2 July 2009.