

PRODUCT MONOGRAPH

 **TIMOPTIC-XE[®]**

timolol maleate ophthalmic gellan solution

**0.25% and 0.5% timolol
Sterile Ophthalmic Solution**

Elevated Intraocular Pressure Therapy

MERCK FROSST CANADA LTD.
16711 Trans Canada Highway
Kirkland QC H9H 3L1
Canada
www.merckfrosst.com

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Table of Contents

| | |
|--|-----------|
| PART I: HEALTH PROFESSIONAL INFORMATION | 1 |
| SUMMARY PRODUCT INFORMATION | 1 |
| INDICATIONS AND CLINICAL USE | 1 |
| CONTRAINDICATIONS | 1 |
| WARNINGS AND PRECAUTIONS | 1 |
| ADVERSE REACTIONS | 3 |
| DRUG INTERACTIONS | 4 |
| DOSAGE AND ADMINISTRATION | 4 |
| OVERDOSAGE | 5 |
| ACTION AND CLINICAL PHARMACOLOGY | 5 |
| STORAGE AND STABILITY | 6 |
| DOSAGE FORMS, COMPOSITION AND PACKAGING | 6 |
| | |
| PART II: SCIENTIFIC INFORMATION | 6 |
| PHARMACEUTICAL INFORMATION | 6 |
| CLINICAL TRIALS | 7 |
| DETAILED PHARMACOLOGY | 7 |
| TOXICOLOGY | 8 |
| BIBLIOGRAPHY | 9 |
| | |
| PART III: CONSUMER INFORMATION | 10 |

TIMOPTIC-XE®

timolol maleate ophthalmic gellan solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/ Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|----------------------------------|--|
| Ophthalmic | Solution, 0.25% and 0.5% timolol | <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

INDICATIONS AND CLINICAL USE

TIMOPTIC-XE® (timolol maleate ophthalmic gellan solution) is indicated for the reduction of elevated intraocular pressure.

In clinical trials TIMOPTIC-XE® has been shown to reduce intraocular pressure in:

- Patients with chronic open-angle glaucoma
- Patients with ocular hypertension
- Aphakic patients having glaucoma, including those wearing contact lenses
- Patients with 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 WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

- Bronchospasm, including bronchial asthma or a history of bronchial asthma or chronic obstructive pulmonary disease.
- Sinus bradycardia; second-and third-degree atrioventricular block; overt cardiac failure; cardiogenic shock.
- Hypersensitivity to any component of this product. For a complete listing of components see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. The same adverse reactions reported with systemic beta-adrenergic blocking agents may occur with topical administration.

TIMOPTIC-XE® should be used with caution in patients subject to spontaneous hypoglycemia or in diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.

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. When TIMOPTIC-XE® is used to reduce elevated intraocular pressure in angle-closure glaucoma they should be used with a miotic and not alone.

Cardiac failure should be adequately controlled before beginning therapy with TIMOPTIC-XE®. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of TIMOPTIC® (timolol maleate ophthalmic solution, USP). These are also potential complications of therapy with TIMOPTIC-XE®.

Because of the potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patient with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC-XE[®], alternative therapy should be considered.

Endocrine and Metabolism

Thyrotoxicosis

β-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of β-adrenergic blocking agents which might precipitate a thyroid storm.

Immune

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. These patients may be more resistant to treatment of anaphylactic reactions with the usual doses of epinephrine since timolol may blunt the beta agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.

Ophthalmologic

Choroidal Detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide or combination) after filtration procedures. Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC[®] (timolol maleate ophthalmic solution, USP) after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least 3 years, no significant difference in mean intra ocular pressure has been observed after initial stabilization.

Contact Lenses

The preservative in TIMOPTIC-XE[®] is benzododecinium bromide. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. For TIMOPTIC-XE[®], studies have not been done in patients wearing contact lenses. However, in a clinical study, the time required to eliminate 50% of the gellan solution from the eye was up to 30 minutes.

Neurologic

Muscle Weakness

β-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Peri-Operative Considerations

Major Surgery

The necessity or desirability of withdrawal of β-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic blocking agents. If necessary during surgery, the effects of β-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Special Populations

Pregnant Women:

TIMOPTIC-XE[®] has not been studied in human pregnancy. The use of TIMOPTIC-XE[®] requires that the anticipated benefit be weighed against possible hazards.

Nursing Women:

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from timolol in nursing 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.

Pediatrics:

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

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

Ocular: Burning and stinging, discharge, foreign body sensation, itching.

The adverse reactions reported for TIMOPTIC® (timolol maleate ophthalmic solution, USP) are potential adverse reactions for TIMOPTIC-XE®. Please refer to the list below.

Body as a Whole: Headache, asthenia, fatigue, chest pain.

Cardiovascular: Aggravation or precipitation of certain cardiovascular pulmonary and other disorders presumably related to effects of systemic beta blockade has been reported (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS). These include bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, palpitation, cardiac arrest, congestive heart failure, edema, claudication, Raynaud's phenomenon, cold hands and feet and in insulin-dependent diabetics masked symptoms of hypoglycemia have been reported rarely.

Digestive: Nausea, diarrhea, dyspepsia, dry mouth.

Hypersensitivity: Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localized and generalized rash.

Immunologic: Systemic lupus erythematosus.

Integumentary: Alopecia, psoriasiform rash or exacerbation of psoriasis.

Nervous System/Psychiatric: Dizziness, depression, insomnia, nightmares, memory loss, increase in signs and symptoms of myasthenia gravis, paresthesia.

Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, cough.

Special Senses: Signs and symptoms of ocular irritation: including burning and stinging, 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, and choroidal detachment following filtration surgery. (see WARNINGS AND PRECAUTIONS).

Tinnitus.

Urogenital: Decreased libido, Peyronie's disease.

Causal Relationship Unknown

The following adverse reactions have been reported but a causal relationship to therapy with TIMOPTIC® has not been established: aphakic cystoid macular edema, nasal congestion, anorexia, CNS effects (e.g., behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances), hypertension, retroperitoneal fibrosis and pseudopemphigoid.

Adverse reactions reported in clinical experience with systemic timolol maleate may be considered potential side effects of ophthalmic timolol maleate.

DRUG INTERACTIONS

Drug-Drug Interactions

Beta-adrenergic Blockers

Patients who are already receiving a beta blocker systemically and who are given TIMOPTIC-XE® should be observed for a potential additive effect on the intraocular pressure or on the known systemic effects of beta blockers (hypotension and/or bradycardia). The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Channel Blockers or Catecholamine-depleting Drugs

The potential exists for additive effects and production of hypotension and/or marked bradycardia when TIMOPTIC-XE® is administered together with an oral calcium channel blocker or catecholamine-depleting drugs such as reserpine.

Clonidine

Oral β -adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the β -adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by β -blocker therapy, the introduction of β -adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

Epinephrine

Although timolol maleate used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with epinephrine has been reported occasionally.

The potential for mydriasis also exists from concomitant therapy with TIMOPTIC-XE® and epinephrine.

Quinidine

Potentiated systemic beta blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Clinical Laboratory Test

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The usual starting dosage is one drop of 0.25% TIMOPTIC-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% TIMOPTIC-XE® in the affected eye(s) once a day.

Invert the closed container and shake once before each use. It is not necessary to shake the container more than once.

If needed, concomitant therapy with miotics, epinephrine and systemically administered carbonic anhydrase inhibitors may be given with TIMOPTIC-XE®. Other topically applied medications should be administered no less than 10 minutes before TIMOPTIC-XE®.

How to Transfer Patients from Other Therapy

When a patient is transferred from TIMOPTIC® (timolol maleate ophthalmic solution, USP) to TIMOPTIC-XE®, TIMOPTIC® should be discontinued after proper dosing on one day, and treatment with the same concentration of TIMOPTIC-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 TIMOPTIC-XE® started on the following day with one drop of 0.25% TIMOPTIC-XE® in the affected eye(s) once a day. The dose may be increased to one drop of 0.5% TIMOPTIC-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% TIMOPTIC-XE® to each affected eye once a day. On the following day, discontinue the previously used antiglaucoma agent and continue TIMOPTIC-XE®. If a greater response is required, substitute one drop of 0.5% TIMOPTIC-XE® for the 0.25% dosage.

Missed Dose

If a dose is missed, it should be applied as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken as usual.

OVERDOSAGE

There have been reports of inadvertent overdosage with TIMOPTIC® (timolol maleate ophthalmic solution, USP) 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).

The following additional therapeutic measures should be considered:

Gastric lavage: If ingested. Studies have shown that timolol does not dialyze readily.

Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.

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

Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

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.

Heart block (second-or third-degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Timolol maleate is a general beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) 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.

Pharmacokinetics

Timolol maleate (S(-) enantiomer) is significantly metabolized after oral and ophthalmic administration. The drug and the metabolites (hydroxyethylamino, hydroxyethylglycolamino derivatives and a third minor metabolite that results from the hydroxylation of a terminal methyl group on the tertiary butylamino moiety) are excreted primarily via the kidney. Based on correlation with debrisoquine metabolism, timolol metabolism is mediated primarily by cytochrome P-450 2D6. Timolol is moderately (<60%) bound to plasma proteins.

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice-daily topical administration of timolol maleate ophthalmic solution 0.5% for 8 days. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

By comparison to plasma concentrations (10 to 20 ng/mL) following oral 5 mg dose, it was estimated that timolol was approximately 50% bio-available systemically following intraocular administration.

STORAGE AND STABILITY

Store at room temperature (15°-25°C). Protect from light and freezing.

The contents of TIMOPTIC-XE® should not be used for more than one month after the date on which the container is first opened.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TIMOPTIC-XE® is a formulation of timolol maleate containing novel delivery vehicle. It is a sterile aqueous solution.

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

Non-medicinal ingredients: gellan gum, mannitol, tromethamine and water for injection. Benzododecinium bromide 0.012% is added as preservative.

Gellan gum used in this formulation contains a highly purified anionic heteropolysaccharide. Aqueous solutions of gellan gum form a clear transparent gel at low polymer concentrations in the presence of cations. The concentration of sodium cation in tears is ideally suited to cause gelation of the material when topically instilled in the conjunctival sac. When TIMOPTIC-XE® contacts the pre-corneal tear film, it becomes a gel. The vehicle of TIMOPTIC-XE®, gellan gum, increases the contact time of the drug with the eye.

TIMOPTIC-XE® is a sterile, colourless to nearly colourless, slightly opalescent, slightly viscous, aqueous ophthalmic solution, supplied in translucent, high-density polyethylene OCUMETER PLUS® ophthalmic dispenser, with a sealed dropper tip, a flexible fluted side area which is depressed to dispense the drops and a 2-piece cap assembly.

The opaque, white, 2-piece cap mechanism punctures the dropper tip seal upon initial use, then locks to provide a single cap during the usage period. Tamper evidence is provided by a safety strip on the container label.

Ophthalmic Gellan Solution TIMOPTIC-XE®, equivalent to 2.5 mg (0.25%) timolol per mL; in 5 mL dispensers, colour-coded with a light blue label on the cap.

Ophthalmic Gellan Solution TIMOPTIC-XE®, equivalent to 5.0 mg (0.5%) timolol per mL; in 5 mL dispensers, colour-coded with a dark blue label on the cap.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

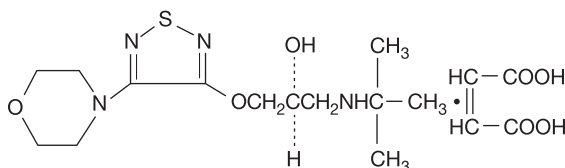
Proper Name: Timolol maleate

Chemical Name: (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)

Molecular formula: C₁₃H₂₄N₄O₃S•C₄H₄O₄

Molecular mass: 432.49

Structural formula:



Physicochemical properties:

Description: Timolol maleate is a beta-adrenergic receptor blocking agent. It possesses an asymmetric carbon atom in its structure and is provided as the levo isomer. It is a white odourless, crystalline powder which is soluble in water, methanol and alcohol.

CLINICAL TRIALS

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

TIMOPTIC® has also been used in patients with glaucoma wearing conventional hard contact lenses, and has generally been well tolerated. TIMOPTIC® has not been studied in patients wearing lenses made with materials other than polymethylmethacrylate.

TIMOPTIC-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 (see WARNINGS AND PRECAUTIONS).

TIMOPTIC® was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. TIMOPTIC-XE® has a systemic safety profile similar to that of TIMOPTIC®, and, as TIMOPTIC®, it is well tolerated. Bradycardia was reported less frequently with TIMOPTIC-XE® than with TIMOPTIC®. In the three studies comparing TIMOPTIC-XE® 0.5% once a day to TIMOPTIC® 0.5% twice a day, TIMOPTIC-XE® did not reduce mean heart rate as much as TIMOPTIC® (see WARNINGS AND PRECAUTIONS). At trough (24 hours post-dose TIMOPTIC-XE®, 12 hours post-dose TIMOPTIC®), the mean reduction was 0.8 beats/minute for TIMOPTIC-XE® and 3.6 beats/minute for TIMOPTIC®; whereas at two hours post-dose, the mean reduction in heart rate was comparable (3.8 beats/minute for TIMOPTIC-XE® and 5 beats/minute for TIMOPTIC®).

There was a higher incidence of transient blurred vision following instillation in patients administered TIMOPTIC-XE®.

DETAILED PHARMACOLOGY

TIMOPTIC® (timolol maleate ophthalmic solution, USP) 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 level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Onset of action of timolol maleate is usually rapid, occurring approximately 20 minutes after topical application on the eye. Maximum reduction of intraocular pressure occurs in one to two hours with TIMOPTIC® whereas it occurs in two to four hours with TIMOPTIC-XE®. Significant lowering of intraocular pressure has been maintained for as long as 24 hours with 0.25% or 0.5% Ophthalmic Solution TIMOPTIC® twice a day and TIMOPTIC-XE® once a day. Repeated observations over a period of three years indicate that the intraocular pressure-lowering effect of TIMOPTIC® is well maintained.

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. 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 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 TIMOPTIC® a refraction might be necessary when these effects of the miotic have passed.

TOXICOLOGY

Ocular effects

No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC® (timolol maleate ophthalmic solution, USP) topically in studies lasting one and two years respectively.

No adverse ocular effects were observed in rabbits and monkeys administered TIMOPTIC-XE® topically in studies lasting one month and 12 months, respectively.

Acute Toxicity (LD₅₀)

| Species and Age | Sex | Route of Administration | LD ₅₀ mg/kg |
|-----------------|-----|-------------------------|------------------------|
| Mouse (A) | F | Oral | 1190 |
| | F | Intravenous | 222 |
| | F | Subcutaneous | 1040 |
| Rat (YA) | M | Oral | 947 |
| | F | Oral | 900 |
| | M | Oral (Fed) | 1800 |
| | M | Intraperitoneal | 390 |
| | F | Intraperitoneal | 383 |
| Rat (W) | M | Oral | 1040 |
| | F | Oral | 969 |
| | M/F | Intraperitoneal | 409 |
| Rat (I) | M/F | Oral | 241 |
| | M/F | Subcutaneous | 143 |
| Rabbit (A) | M/F | Oral | 485 |
| | M/F | Subcutaneous | 34 |

(A)=Adult; (YA)=Young Adult; (W)=Weanling; (I)=Infant

Signs of toxicity occurred immediately after intravenous administration and from 10 to 30 minutes following oral, intraperitoneal or subcutaneous administration. The signs observed included lacrimation, ataxia, tremors and bradypnea. Clonic convulsions usually preceded death.

The oral LD₅₀ of gellan gum is greater than 5 000 mg/kg in rats.

Oral Interactions Studies

Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no influence on the toxicity of timolol maleate. Timolol maleate had no effect on the hypoprothrombinemia induced by bishydroxycoumarin in the dog.

Subacute Toxicity

In rats treated with 100 to 400 mg/kg/day for seven weeks, excessive salivation seen 5 to 10 minutes after dosing had a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptyalism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg/day or higher, were lethal to some animals. Low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas. Similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs in a 15-day intravenous toxicity study.

Chronic Toxicity

Rats

Timolol was administered orally to rats at dose levels of 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident.

Dogs

In a 54-week oral study timolol was administered at doses of 5, 10 and 25 mg/kg/day. Body weight and food consumption were normal and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day.

Tumorigenic Tests

Lifetime studies with timolol have been completed in rats at oral doses of 25, 100 and 300 mg/kg/day and in mice at oral doses of 5, 50 and 500 mg/kg/day. In male and female rats and male mice at all dose levels, and in female mice at dose levels of 5 and 50 mg/kg/day, timolol demonstrated no carcinogenic effect. There was a slight increase in the incidence of mammary adenocarcinomas in female mice that received 500 mg/kg/day (about 500 times the maximum recommended human oral dose, on a mg/kg basis). Timolol caused dose-related elevations of serum prolactin in female mice at doses of 100 mg/kg/day or more, but only very slight transient elevations were found in male mice at doses of 500 mg/kg/day. Since numerous studies have demonstrated that drugs which cause elevations of serum prolactin are associated with mammary tumors in rodents, the mammary tumors in the female mice in the highest dosage group of this study were considered to have resulted from an increased serum prolactin. In humans, no such association between serum prolactin and mammary carcinoma has been established.

Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Reproductive Studies

Teratogenic studies in the mouse and rabbit at dose levels of 2 to 50 mg/kg/day did not reveal evidence of teratogenicity but did suggest embryotoxicity at the highest dose. Oral administration of timolol maleate to rats at dose levels of 4 to 100 mg/kg/day did not adversely affect the fertility of male or female rats, their reproductive performance, or the development of their offspring.

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PART III: CONSUMER INFORMATION

TIMOPTIC-XE®

timolol maleate ophthalmic gellan solution

This leaflet is part III of a three-part “Product Monograph” published when TIMOPTIC-XE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TIMOPTIC-XE®. Contact your physician or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

TIMOPTIC-XE® is the brandname for the medication timolol maleate ophthalmic gellan solution. TIMOPTIC-XE® is an ophthalmic solution of a beta-blocking drug which lowers the pressure in the eye for conditions such as glaucoma and ocular hypertension and is only available through a prescription by your physician.

Remember - This medicine is prescribed for the particular condition that you have. **Do not give this medicine to other persons, nor use it for any other condition.**

What it does:

The active ingredient timolol maleate is a beta-blocking drug. It helps lower the pressure in the eye.

When it should not be used:

Do not use TIMOPTIC-XE® if you:

- are allergic to any of its components
- have asthma or have ever had asthma
- have chronic obstructive lung disease
- have certain heart diseases or conditions
- are breast feeding or intend to breast feed.

What the medicinal ingredient is:

Timolol maleate.

What the important nonmedicinal ingredients are:

gellan gum, mannitol, tromethamine and water for injection. Benzododecinium bromide is added as preservative.

What dosage forms it comes in:

TIMOPTIC-XE® is a sterile eye drop containing timolol as the active ingredient. This eyedrop also contains a new delivery vehicle which is obtained from a natural substance. This vehicle allows the eye drop to form a clear transparent gel when it contacts the eye.

Ophthalmic Gellan Solution TIMOPTIC-XE®, equivalent to 2.5 mg (0.25%) timolol per mL; in 5 mL dispensers, colour-coded with a light blue label on the cap.

Ophthalmic Gellan Solution TIMOPTIC-XE®, equivalent to 5.0 mg (0.5%) timolol per mL; in 5 mL dispensers, colour-coded with a dark blue label on the cap.

WARNINGS AND PRECAUTIONS

This medicine may not be suitable for some patients. So, tell your physician if you think **any** of the following applies to you:

- If you have any medical problems now or have had any in the past, especially asthma and other lung problems or heart problems;
- If you have any allergies to any medications;
- TIMOPTIC-XE® contains the preservative benzododecinium bromide. If you wear contact lenses, you should consult your physician or pharmacist before using TIMOPTIC-XE®. Do not administer while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.
- If you had past thyroid problems.
- If you had past eye problems such as choroidal detachment.
- If you had problems or develop problems with blood flow to the brain.
- If you are pregnant or intend to become pregnant;
- If you are breast feeding or intend to breast feed. Timolol has been detected in human breast milk. Discuss with your physician.

TIMOPTIC-XE® IS NOT RECOMMENDED FOR CHILDREN.

INTERACTIONS WITH THIS MEDICATION

Your physician also needs to know about drugs (including eye drops) that you are using or plan to use, including drugs obtained without a prescription. This is particularly important if you are taking medicine to lower blood pressure or to treat heart disease or depression including beta-blockers such as atenolol, epinephrine, quinidine, calcium channel blockers or catecholamine depleting drugs such as reserpine.

PROPER USE OF THIS MEDICATION

Read the following information carefully. **If you need any explanations, or further information, ask your physician or pharmacist.**

- Do not start taking any other medicines unless you have discussed the matter with your physician or pharmacist.
- If you suspect that TIMOPTIC-XE® is causing an allergic reaction (for example, skin rash or itching), stop its use and contact your physician as soon as possible.
- If you develop any eye irritation or any new eye problems such as redness of the eye or swelling of the eyelids, contact your physician immediately.
- If you are using TIMOPTIC-XE® with another eyedrop, the drops should be instilled at least 10 minutes apart.

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- Do not change the dosage recommended by your physician. If you must stop treatment, contact your physician immediately.
- Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.
- Contact your physician without delay if you have ocular surgery or develop a condition that was not present at the time this medication was prescribed (e.g., trauma, an infection, etc.).
- The contents of the container should not be used for more than one month after the date on which the container is first opened.

Usual Adult dose:

The appropriate dosage and duration of treatment will be established by your physician.

The usual dose is one drop in the affected eye(s) once a day.

Overdose

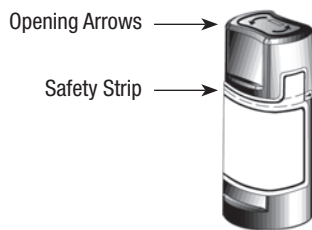
If you put too many drops in your eye or swallow any of the contents of the bottle, you should contact your physician immediately.

Missed Dose:

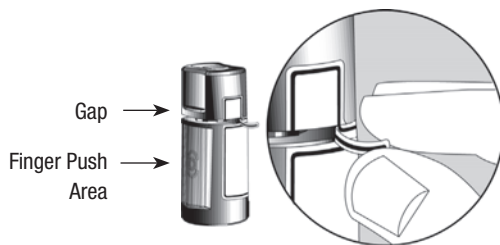
It is important to apply TIMOPTIC-XE® as prescribed by your physician. If you miss a dose, apply it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

INSTRUCTIONS FOR USE

1. Before using the medication for the first time, be sure the Safety Strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.

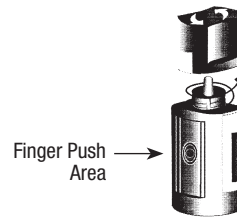


2. Tear off the Safety Strip to break the seal.

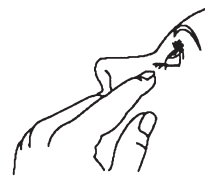


3. Invert the closed bottle and shake ONCE before each use. (It is not necessary to shake the bottle more than once.)

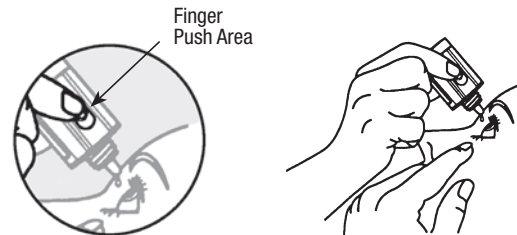
4. To open the bottle, unscrew the cap by turning as indicated by the arrows on the top of the cap. When opening the bottle for the first time, do not pull the cap directly up and away from the bottle. Pulling the cap directly up will prevent your container from operating properly.



5. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.



6. Invert the bottle and press lightly with the thumb or index finger over the "Finger Push Area" (as shown) until a single drop is dispensed into the eye as directed by your physician.



DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.

Ophthalmic medications, if handled improperly, can become contaminated by common bacteria known to cause eye infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic medications. If you think your medication may be contaminated, or if you develop an eye infection, contact your physician immediately concerning continued use of this bottle.

7. If drop dispensing is difficult after opening for the first time, replace the cap on the bottle and tighten (DO NOT OVERTIGHTEN) and then remove by turning the cap in the opposite direction as indicated by the arrows on the top of the cap.
8. Repeat steps 5 & 6 with the other eye if instructed to do so by your physician.
9. Replace the cap by turning until it is firmly touching the bottle. The arrow on the left side of the cap must be aligned with the arrow on the left side of the bottle label for proper closure. Do not overtighten or you may damage the bottle and cap.

10. The dispenser tip is designed to provide a single drop; therefore, do NOT enlarge the hole of the dispenser tip.
11. After you have used all doses, there will be some TIMOPTIC-XE® left in the bottle. You should not be concerned since an extra amount of TIMOPTIC-XE® has been added and you will get the full amount of TIMOPTIC-XE® that your physician prescribed. Do not attempt to remove excess medicine from the bottle.
12. Tell your physician if you wear contact lenses. Depending on the type of lense, your physician may advise that you re-insert your contact lenses not earlier than 15 minutes after application of TIMOPTIC-XE®.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Any medicine may have unintended or undesirable effects, so-called side effects. Although not all of these side effects may occur, if they do occur, you may need medical attention.
- You may experience eye symptoms such as itching, burning and stinging, dry eyes, redness of the eye, foreign body sensation or visual changes, such as double vision.
- Other side effects may also occur rarely, and some of these may be serious. These may include shortness of breath.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic gravis.
- Your physician or pharmacist has a complete list of the possible side effects from this medication. Please tell your physician or pharmacist promptly about any unusual symptom.
- Your vision may be temporarily blurred for 30 seconds to 5 minutes immediately after putting TIMOPTIC-XE® in your eye. Make sure that your vision is clear before you drive a motor vehicle or operate machinery.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your physician or pharmacist | | Stop taking drug and call your physician or pharmacist |
|------------------|--|--|--------------|--|
| | | Only if severe | In all cases | |
| Uncommon | slow heartbeat | | | ✓ |
| Rare | Heart effects such as irregular heartbeat, heart block, low blood pressure | | | ✓ |
| | Allergic reactions with symptoms such as swelling of the mouth and throat, shortness of breath, hives, severe itching and rash | | | ✓ |

This is not a complete list of side effects. For any unexpected effects while taking TIMOPTIC-XE®, contact your physician or pharmacist.

HOW TO STORE IT

Store at room temperature 15° - 25°C. Protect from light. Avoid freezing.

Do not use this medicine after the date shown on the container.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345
 Toll-free fax: 1-866-678-6789
 By email: cadmp@hc-sc.gc.ca
 By regular mail:
 National AR Centre
 Marketed Health Products Safety and Effectiveness Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa, ON K1A 0K9

or Merck Frosst Canada Ltd. by:
 Toll-free telephone: 1-800-567-2594
 Toll-free fax: 1-877-428-8675
 By regular mail:
 Merck Frosst Canada Ltd.
 P.O. Box 1005
 Pointe-Claire - Dorval, QC H9R 4P8

NOTE: Before contacting Health Canada or Merck Frosst, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
<http://www.merckfrosst.com>

or by contacting the sponsor, Merck Frosst Canada Ltd., at: 1-800-567-2594.

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KIRKLAND, QUEBEC, CANADA

