TIMOPTIC® TIMOPTIC-XE® Merck Frosst Timolol Maleate
Elevated Intraocular Pressure Therapy

Action and Clinical

Timolol 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 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 P450 2D6. Timolol is moderately (<60%) bound to plasma proteins.

In a study of plasma drug concentration in 6 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% bioavailable systemically following intraocular administration.

Indications And Clinical Uses:

The reduction of elevated intraocular pressure.

In clinical trials it 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 Precautions).

**Contra-Indications:**

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.

**Warnings in Clinical States:**

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

Use 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 has little or no effect on the pupil. When Timoptic or 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 and 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. These are also potential complications of therapy with Timoptic-XE.
Precautions:

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 timolol 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 intraocular pressure has been observed after initial stabilization.

Contact Lenses: The preservative in Timoptic is benzalkonium chloride and in Timoptic-XE benzododecinium bromide. Both preservatives are quaternary ammonium compounds that may be absorbed by soft contact lenses. For Timoptic, the lenses should be removed before application of the drops and not re-inserted earlier than 15 minutes after use. 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.

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.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or norepinephrine.

Thyrotoxicosis: Beta-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 beta-adrenergic blocking agents which
might precipitate a thyroid storm.

**Muscle Weakness:** Beta-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.

**Pregnancy:** Timolol has not been studied in human pregnancy. The use of timolol requires that the anticipated benefit be weighed against possible hazards.

**Lactation:** 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.

**Children:** Safety and effectiveness in children have not been established.

**Drug Interactions:**

**Beta-adrenergic Blockers:** Patients who are already receiving a beta-blocker systemically and who are given Timoptic or 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 2 topical beta-adrenergic blocking agents is not recommended.

**Epinephrine:** Although timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Timoptic and 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) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P450 enzyme, CYP2D6.

**Calcium Channel Blockers or Catecholamine-depleting Drugs:** The potential exists for additive effects and production of hypotension and/or marked bradycardia when Timoptic or Timoptic-XE is administered together with an oral calcium entry blocker or
catecholamine-depleting drugs such as reserpine.

Information to Be Provided to the Patient: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

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

There have been reports of bacterial keratitis associated with the use of 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.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, or cardiac failure should be advised not to take this product (see Contraindications).

If more than one topical ophthalmic drug is being utilized, the drugs should be administered at least 10 minutes apart.

Patients Wearing Contact Lenses: Timoptic: Patients should be instructed to remove their lenses before application of the drops and not to re-insert the lenses earlier than 15 minutes after use.

Timoptic-XE: Patients should be instructed to consult their physician before using Timoptic-XE.

The contents should not be used for more than 1 month after the date on which the container is first opened.

**Adverse Reactions:**

Timolol maleate ophthalmic solution is usually well tolerated.

The following adverse reactions have been reported with ocular administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed.
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 Precautions).

Tinnitus.

Integumentary: alopecia, psoriasiform rash or exacerbation of psoriasis.

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

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 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. In clinical trials, slight reduction of the resting heart rate in some patients (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed.

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

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

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

Digestive: nausea, diarrhea, dyspepsia, dry mouth.

Urogenital: decreased libido, Peyronie's disease.

Immunologic: systemic lupus erythematosus.

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.

Timoptic-XE: Timolol maleate ophthalmic gellan solution is usually well tolerated. The most frequent (6%) drug-related complaint in clinical trials 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.

Potential Adverse Reactions: The adverse reactions listed above under Timoptic are potential adverse reactions for Timoptic-XE.

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

**Symptoms And Treatment Of Overdose:**

There have been reports of inadvertent overdosage with Timoptic 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 Effects).

The following additional therapeutic measures should be considered: (1) Gastric lavage: if ingested. Studies have shown that timolol does not dialyze readily. (2) Symptomatic bradycardia: use atropine sulfate i.v. in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, i.v. isoproterenol HCl should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered. (3) Hypotension: use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or norepinephrine. In refractory cases the use of glucagon HCl has been reported to be useful. (4) Bronchospasm: use isoproterenol HCl. Additional therapy with aminophylline may be considered. (5) Acute cardiac failure: conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of i.v. aminophylline is suggested. This may be followed if necessary by glucagon HCl which has been reported
to be useful. (6) Heart block (second- or third-degree): use isoproterenol HCl or a transvenous cardiac pacemaker.

Dosage And Administration:

Timoptic: Recommended dosage is 1 drop of 0.25% solution in the affected eye twice a day.

If clinical response is not adequate, dosage may be changed to 1 drop of 0.5% solution in each affected eye twice a day. If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with Timoptic. The use of two topical beta-adrenergic blocking agents is not recommended (see Precautions).

Since in some patients the pressure-lowering response to Timoptic may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment.

If the intraocular pressure is maintained at satisfactory levels, many patients can be placed on once-a-day therapy. Because of naturally occurring diurnal variations in intraocular pressure, satisfactory response is best determined by measuring the intraocular pressure at different times during the day.

How to Transfer Patients from Other Therapy: 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 started on the following day with 1 drop of 0.25% Timoptic in the affected eye(s) twice a day. The dose may be increased to 1 drop of 0.5% Timoptic twice 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 already being used and add 1 drop of 0.25% Timoptic in each affected eye twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with Timoptic. If a higher dosage of Timoptic is required, substitute 1 drop of 0.5% solution in each affected eye twice a day.

When a patient is transferred from several concomitantly administered antiglaucoma agents, individualization is required. The physician may be able to discontinue some or all of the other antiglaucoma agents. Adjustments should involve one agent at a time.
Clinical trials have shown the addition of Timoptic to be useful in patients who respond inadequately to the maximum tolerable antiglaucoma drug therapy.

Timoptic-XE: The usual starting dose is 1 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 1 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 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 1 drop of 0.25% Timoptic-XE in the affected eye(s) once a day. The dose may be increased to 1 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 1 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 1 drop of 0.5% Timoptic-XE for the 0.25% dosage.

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.
**Availability And Storage:**

Timoptic: Each mL of clear, colorless to light yellow, sterile, isotonic, buffered, aqueous ophthalmic solution contains: timolol maleate equivalent to 2.5 mg (0.25%) or 5 mg (0.5%) timolol. Nonmedicinal ingredients: benzalkonium chloride, monobasic and dibasic sodium phosphate, sodium hydroxide and water for injection. White, opaque, plastic Ocumeter ophthalmic dispensers, color-coded with light blue (2.5 mg) or yellow (5 mg) cap and label, of 10 mL with controlled drop tip. Store at room temperature (15 to 25°C). Protect from light.

Timoptic-XE: Each mL of sterile, colorless to nearly colorless, slightly opalescent, slightly viscous, aqueous ophthalmic solution contains: timolol maleate equivalent to 2.5 mg (0.25%) or 5 mg (0.5%). Nonmedicinal ingredients: benzododecinium bromide, gellan gum, mannitol, tromethamine. Dispensers, color-coded with light blue (2.5 mg) or yellow (5 mg) cap and label, of 2.5 and 5 mL. Store at room temperature (15 to 25°C). Protect from light and freezing.

The contents should not be used for more than 1 month after the date on which the container is first opened.