

PRODUCT MONOGRAPH

 **TIMOPTIC**<sup>®</sup>

**timolol maleate ophthalmic solution, USP**

**0.5% timolol  
Sterile Ophthalmic Solution**

Elevated Intraocular Pressure Therapy

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# TIMOPTIC®

timolol maleate ophthalmic solution, USP

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

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

### INDICATIONS AND CLINICAL USE

TIMOPTIC® (timolol maleate ophthalmic solution, USP) is indicated for the reduction of elevated intraocular pressure.

In clinical trials TIMOPTIC® 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

- 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.
- 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.

### 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® 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® 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®. 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 timolol maleate ophthalmic solutions.

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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> is benzalkonium chloride. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. Therefore, TIMOPTIC<sup>®</sup> should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

## **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<sup>®</sup> has not been studied in human pregnancy. The use of TIMOPTIC<sup>®</sup> 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® 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.

### **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.

### **Potential Adverse Reactions**

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® 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® is administered together with an oral calcium channel blocker or catecholamine-depleting drugs such as reserpine.

#### **Clonidine**

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

#### **Epinephrine**

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

#### **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**

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 dosage is one drop of TIMOPTIC® in the 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 WARNINGS AND 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 with TIMOPTIC®.

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 one drop of TIMOPTIC® in the affected eye(s) twice a day.

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 one drop of TIMOPTIC® in each affected eye twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with TIMOPTIC®.

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.

### **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® 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.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

TIMOPTIC® is supplied as a sterile, isotonic, buffered, aqueous solution. Each mL contains 5 mg of timolol (6.8 mg of timolol maleate).

**Non-medicinal ingredients:** monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and water for injection. Benzalkonium chloride 0.01% is added as preservative.

TIMOPTIC® is a clear, colourless to light yellow 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 Solution TIMOPTIC®, equivalent to 5 mg (0.5%) timolol per mL; in 10 mL dispensers, colour-coded with a dark pink label on the cap.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

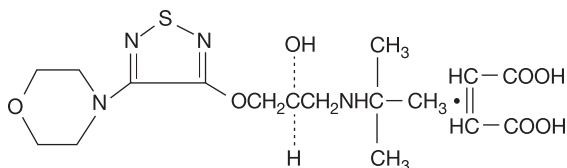
**Proper name:** Timolol maleate

**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:** C<sub>13</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>S•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

**Molecular mass:** 432.49

**Structural formula:**



**Physicochemical properties:**

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

TIMOPTIC® was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. Bradycardia was reported with TIMOPTIC® (see WARNINGS AND PRECAUTIONS). At trough (12 hours post-dose), the mean reduction was 3.6 beats/minute. At two hours post-dose, the mean reduction in heart rate was 5 beats/minute.

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.

## DETAILED PHARMACOLOGY

TIMOPTIC® 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. 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. 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® topically in studies lasting one and two years respectively.

### Acute Toxicity (LD<sub>50</sub>)

Species and Age	Sex	Route of Administration	LD <sub>50</sub> 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.

## **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.

## BIBLIOGRAPHY

1. Berke SJ, Bellows AR, Shingleton BJ, Richter CU, Hutchinson BT. Chronic and recurrent choroidal detachment after glaucoma filtering surgery. *Ophthalmol* 1987;94(2):154-62.
2. Dinai Y, Sharir M, Navey (Floman) N, Halkin H. Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985;103(6): 890-1.
3. Edeki TI, He H, Wood AJJ. Pharmacogenetic explanation for excessive  $\beta$ -blockade following timolol eye drops. *JAMA* 1995;274(20):1611-3.
4. Higginbotham EJ. Topical  $\beta$ -adrenergic antagonists and quinidine: A risky interaction. *Arch Ophthalmol* 1996;114(6):745-6.
5. Kaila R, Huupponen R, Karhuvaara S, Havula P, Scheinin M, Lisalo E, Salminen L.  $\beta$ -Blocking effects of timolol at low plasma concentrations. *Clin Pharmacol* 1991;49(1):53-8.
6. Katz IM, Hubbard WA, Getson AJ, Gould LA. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. *Invest Ophthalmol* 1976;15(6): 489-92.
7. Katz IM, Kulaga SF, Gould AL, Miller IM, Clineschmidt CM, Wittreich JM. Long-term tolerability and efficacy of timolol ophthalmic solution. *Glaucoma* 1987;9:84-8.
8. Mackie JA, Seal DV, Pescod JM. Beta-adrenergic receptor blocking drugs: tear lysozyme and immunological screening for adverse reaction. *Br J Ophthalmol* 1977; 61:354-9.
9. Rozier A, Mazuel C, Grove J, Plazonnet B. GELRITE: A novel, ion-activated, *in situ* Gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. *Intl J Pharmaceut* 1989;57:163-68.
10. Samples JR, Meyer SM. Use of ophthalmic medications in pregnant and nursing women. *Am J of Ophthalmol* 1988;106(5):616-23.
11. Toogood JH. Beta-blocker therapy and the risk of anaphylaxis. *Can Med Assoc J* 1987;136(9):929-33.
12. Vela MA, Campbell DG. Hypotony and ciliochoroidal detachment following pharmacologic aqueous suppressant therapy in previously filtered patients. *Ophthalmol* 1985;92(1):50-7.
13. Yablonski ME, Zimmerman TJ, Waltman SR, Becker B. A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics. *Exp Eye Res* 1978;27:135-42.
14. Zimmerman TJ, Harbin R, Pett M, Kaufman HE. Timolol and facility of outflow. *Invest Ophthalmol Vis Sci* 1977;16(7):623-4.
15. Zimmerman TJ, Kaufman HE. Timolol a  $\beta$ -adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977;95:601-4.
16. Zimmerman TJ, Kaufman HE. Timolol: A new drug for the treatment of Glaucoma? Symposium on Ocular Therapy 1977;10:69-76.
17. Zimmerman TJ, Kaufman HE. Timolol: Dose response and duration of action. *Arch Ophthalmol* 1977;95: 605-7.
18. Zimmerman TJ. Timolol maleate - a new glaucoma medication? *Invest Ophthalmol Vis Sci* 1977;16(8): 687-8.

PART III: CONSUMER INFORMATION

**TIMOPTIC®**

timolol maleate ophthalmic solution, USP

This leaflet is part III of a three-part “Product Monograph” published when TIMOPTIC® 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®. Contact your physician or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**

What the medication is used for:

TIMOPTIC® is the brandname for the medication timolol maleate ophthalmic solution available **only on prescription** through your physician. TIMOPTIC® 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® 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:

Monobasic and dibasic sodium phosphate, sodium hydroxide, and water for injection. Benzalkonium chloride is added as a preservative

What dosage forms it comes in:

TIMOPTIC® (timolol maleate) ophthalmic solution is a sterile eye drop.

Ophthalmic Solution TIMOPTIC®, equivalent to 5 mg (0.5%) timolol per mL; in 10 mL dispensers, colour-coded with a dark pink 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® contains benzalkonium chloride as a preservative. This preservative may be absorbed by soft contact lenses. If you wear soft contact lenses, consult your physician before using TIMOPTIC®. 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® 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® is causing an allergic reaction (for example, skin rash or redness and itching of the eye), 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® with another eyedrop, the drops should be instilled at least 10 minutes apart.
- Do not change the dosage of the drug without consulting 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 (eg. trauma, an infection, etc.).

**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) in the morning and in the evening.

**Overdose:**

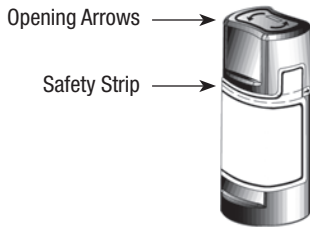
If you put too many drops in your eye or swallow the contents of the bottle, you should contact your physician immediately.

**Missed Dose:**

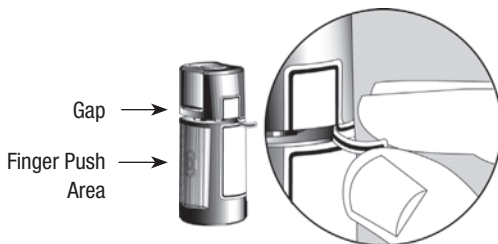
It is important to apply TIMOPTIC® as prescribed by your physician. If you miss a dose, apply it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

**INSTRUCTIONS FOR USE**

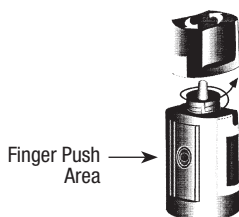
1. Before using the medication for the first time, be sure the Safety Strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.



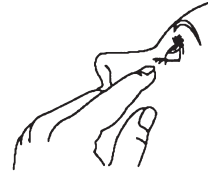
2. Tear off the Safety Strip to break the seal.



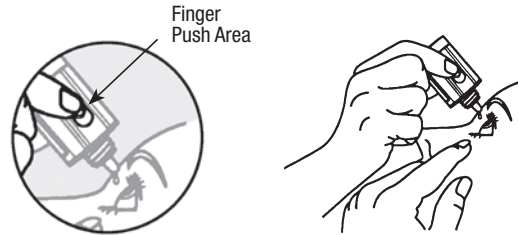
3. To open the bottle, unscrew the cap by turning as indicated by the arrows on the top of the cap. Do not pull the cap directly up and away from the bottle. Pulling the cap directly up will prevent your dispenser from operating properly.



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



5. Invert the bottle, grasping it with the thumb or index finger over the Finger Push Area as shown. Press lightly 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.

6. 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 top of the cap.
7. Repeat steps 4 & 5 with the other eye if instructed to do so by your physician.
8. 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.
9. The dispenser tip is designed to provide a single drop; therefore, do NOT enlarge the hole of the dispenser tip.
10. After you have used all doses, there will be some TIMOPTIC® left in the bottle. You should not be concerned since an extra amount of TIMOPTIC® has been added and you will get the full amount of TIMOPTIC® that your physician prescribed. Do not attempt to remove excess medicine from the bottle.
11. 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®.

## 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 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 myasthenia 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.
- There are side effects of TIMOPTIC® that may affect some patients' ability to drive and use machines.

## 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®, contact your physician or pharmacist.***

## HOW TO STORE IT

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

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](mailto: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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[www.merckfrosst.com](http://www.merckfrosst.com)



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