PRODUCT MONOGRAPH

Pr T-LO
Timolol Ophthalmic Solution, USP
0.25%, 0.5% w/v (as timolol maleate)

and

Pr TIMOLOL MALEATE-EX
Timolol Ophthalmic Gel Forming Solution
0.25%, 0.5% w/v (as timolol maleate)

THERAPEUTIC CLASSIFICATION:
Antiglaucoma Preparations and Miotics

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PRODUCT MONOGRAPH

Pr T-LO
Timolol Ophthalmic Solution, USP

and

Pr TIMOLOL MALEATE-EX
Timolol Ophthalmic Gel Forming Solution

ACTIONS AND CLINICAL PHARMACOLOGY

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.

T-LO and TIMOLOL MALEATE-EX, when applied topically in the eye, has the action of reducing elevated as well as normal intraocular pressure (IOP), whether or not associated with glaucoma. The onset of reduction in IOP following administration of T-LO can usually be detected within 30 minutes after a single dose. The maximum effect usually occurs in one to two hours. Significant lowering of IOP has been maintained for periods as long as 24 hours with 0.25% or 0.5% T-Lo twice a day and 0.25% or 0.5% TIMOLOL MALEATE-EX once per day. Unlike miotics, T-LO and TIMOLOL MALEATE-EX reduce IOP with little or no effect on accommodation or pupil size.

INDICATIONS AND USAGE

T-LO is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with:

- Chronic open glaucoma.
- Ocular hypertension.
- Aphakic patients with glaucoma, including those wearing contact lenses.
- Narrow angles and a history of spontaneous or iatrogenically-induced narrow-angle closure in the opposite eye in whom reduction of IOP is necessary (see WARNINGS AND PRECAUTIONS).

TIMOLOL MALEATE-EX is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with:

- Chronic open-angle glaucoma.
- Ocular hypertension.

Pediatrics (< 18 years of age):
T-LO and TIMOLOL MALEATE-EX are not recommended for use in children or adolescents. The safety and effectiveness of T-LO and TIMOLOL MALEATE-EX in pediatric patients < 18 years of age have not been established.

CONTRAINDICATIONS

T-LO and TIMOLOL MALEATE-EX are contraindicated in patients with:

- Hypersensitivity to timolol or any ingredient in the formulation or component of the container (see Composition; Availability of Dosage Forms).
- Hypersensitivity to other beta-blockers.
- Bronchospasm, including bronchial asthma, a history of bronchial asthma, or chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second and third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.

WARNINGS AND PRECAUTIONS

General
FOR TOPICAL OPHTHALMIC USE ONLY.

T-LO and TIMOLOL MALEATE-EX contain timolol, a beta-adrenergic blocking agent. As with other topically applied ophthalmic agents, timolol may be absorbed systemically. The same types of cardiovascular, pulmonary and other adverse reactions reported with systemic beta-adrenergic blocking agents may occur with topical ophthalmic administration.

Beta-adrenergic blocking agents should be administered 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. They may also mask the signs of hyperthyroidism.

Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms, such as diplopia, ptosis and generalized weakness.

The effect on intraocular pressure (IOP) or the known effects of systemic beta-blockade may be potentiated when T-LO or TIMOLOL MALEATE-EX is given to patients already receiving an oral beta-adrenergic blocking agent. The response of these patients should be closely observed. The use of two local beta-adrenergic blocking agents is not recommended.

Cardiovascular
Cardiac reactions, and rarely, death in association with cardiac failure, have been reported following administration of timolol maleate.

T-Lo and TIMOLOL MALEATE-EX are not recommended for use in patients with cardiovascular diseases (e.g., coronary heart disease, Prinzmetal's angina, and cardiac failure) and hypotension, as it can cause worsening of Prinzmetal's angina, severe peripheral and central nervous system disorders, and hypotension. Therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and for adverse reactions.

Caution is advised when using T-LO or TIMOLOL MALEATE-EX in patients with severe peripheral circulatory disturbances/disorders, such as severe forms of Raynaud's disease or Raynaud's syndrome.

Immune

Anaphylactic Reactions: 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 to such allergens, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. In such cases, alternatives to epinephrine should be considered.

Ophthalmologic

In patients with angle-closure glaucoma, the immediate objective of treatment is to re-open the angle. This requires constricting the pupil with a miotic. T-LO and TIMOLOL MALEATE-EX have little or no effect on the pupil. When T-LO or TIMOLOL MALEATE-EX is used to reduce elevated intraocular pressure in angle-closure glaucoma, they should be used with a miotic and not alone.

As with the use of other anti-glaucoma drugs, diminished responsiveness to T-LO after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure (IOP) has been observed after initial stabilization. In a long-term clinical trial of 157 patients, TIMOLOL MALEATE-EX 0.5% once daily maintained IOP reductions over the one year study period.

T-LO contains the preservative benzalkonium chloride, which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to instillation of T-LO and wait at least 15 minutes after dosing before re-inserting contact lenses.

Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use.

TIMOLOL MALEATE-EX contains the preservative, benzododecinium bromide, which is a quaternary ammonium compound that may be absorbed by soft contact lenses. Studies have not

been performed with TIMOLOL MALEATE-EX in patients wearing contact lenses. Patients should be instructed to consult with their physician prior to use.

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

T-LO and TIMOLOL MALEATE-EX may cause temporary blurred vision or other visual disturbances that can affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Peri-Operative Considerations

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects, such as that of adrenaline. The anesthesiologist should be informed if and when patients are receiving timolol.

Respiratory

Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of timolol maleate.

Sexual Function/Reproduction

There are no data on the effect of timolol on human fertility.

Drug Interactions

Mydriasis resulting from concomitant use of ophthalmic beta-blockers, such as timolol, and adrenaline (epinephrine) has been reported occasionally.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic solutions with beta-blockers, such as timolol, are administered concomitantly with oral calcium channel blockers, quinidine, catecholamine-depleting drugs, beta-adrenergic blocking agents, antiarrhythmics (e.g. amiodarone, digitalis glycosides or parasympathomimetics).

Potentiated systemic beta-blockade (e.g. decreased heart rage) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, cimetidine, fluoxetine, paroxetine) and timolol.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-adrenergic blocking agents.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies in pregnant women. Epidemiological studies have not revealed malformative effects, but show a risk of intrauterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g., bradycardia, hypotension, respiratory distress and hypoglycemia) have been observed in the neonate when beta-blockers have been administered until delivery. T-LO and TIMOLOL MALEATE-EX should not be used during pregnancy unless clearly necessary. If T-LO or TIMOLOL-MALEATE-EX is administered until delivery, the neonate should be carefully monitored during the first days of life.

Nursing Women:

T-LO and TIMOLOL MALEATE-EX should not be used by nursing women. Beta-blockers are excreted in breast milk, having the potential to cause serious undesirable effects in the breastfeeding infant.

Pediatrics (< 18 years of age):

The safety and effectiveness of T-LO or TIMOLOL MALEATE-EX have not been established in children. T-LO and TIMOLOL MALEATE-EX are not recommended for use in children or adolescents.

ADVERSE EFFECTS

Adverse Drug Reaction Overview

In clinical studies with T-LO, the most common ocular adverse reactions reported were ocular hyperemia (5.1%) and eye irritation (2.4%). Other ocular adverse reactions occurring with a frequency of at least 1% were eye pain, ocular discomfort, and vision blurred.

In clinical studies with TIMOLOL MALEATE-EX, the most common ocular adverse events were blurred vision (4.1%) and discomfort (2.9%). Other ocular adverse events occurring with a frequency of at least 1% were: blepharitis, hyperemia, pruritus, foreign body sensation, lid margin crusting and tearing.

T-LO and TIMOLOL MALEATE-EX are usually well tolerated.

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.*

MedDRA SOC and PT (version 15.1)	Frequency Category	Pooled Total (N=2632)	
		N	%
Eye disorders			
Ocular hyperemia	Common	133	5.05
Eye irritation	Common	63	2.39
Eye pain	Common	40	1.52
Ocular discomfort (including foreign body sensation in eyes and abnormal sensation in eyes)	Common	34	1.29
Vision blurred	Common	32	1.22

Less Common Clinical Trial Adverse Drug Reactions with T-Lo (<1%)

Cardiac disorders: bradycardia, myocardial infarction
Eye disorders: corneal erosion, punctate keratitis, keratitis, iritis, conjunctivitis, blepharitis, reduced visual acuity (including ptosis and refractive changes due to withdrawal of miotic therapy in some cases), photophobia, dry eye, lacrimation increased, eye discharge, eye pruritus, eyelid margin crusting, anterior chamber inflammation, eyelid edema, conjunctival hyperemia, uveitis, diplopia, asthenopia, eczema of eyelids, erythema of eyelid, eyelid pruritus, conjunctival edema, corneal pigmentation
Gastrointestinal disorders: dysgeusia, dyspepsia, abdominal discomfort, dry mouth
General disorders and administration site conditions: fatigue, asthenia, chest discomfort
Nervous system disorders: headache, cerebral ischemia, dizziness, migraine
Psychiatric disorders: depression
Respiratory, thoracic and mediastinal disorders: asthma, bronchitis, dyspnea, chronic obstructive pulmonary disease, bronchospasm, cough, wheezing, nasal congestion
Skin and subcutaneous tissue disorders: swelling face, erythema
Vascular disorders: hypotension, blood pressure increased, edema peripheral, peripheral coldness

Causal Relationship Unknown
The following adverse reactions have been reported but a causal relationship to therapy with T-LO has not been established: anorexia, aphakic cystoid, CNS effects (e.g., anxiety, confusion, disorientation, hallucinations, nervousness, somnolence and other psychic disturbances), dry mouth, dyspepsia, hypertension, macular edema, nasal congestion, and retroperitoneal fibrosis.

The adverse reactions listed for T-LO are potential adverse reactions for TIMOLOL MALEATE-EX.

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

Post-Market Adverse Drug Reactions

Eye disorders: choroidal detachment (following filtration surgery), eyelid ptosis
Cardiac disorders: cardiac arrest, atrioventricular block (complete, lower degree or aggravation), arrhythmia, palpitations
Gastrointestinal disorders: vomiting, diarrhea, nausea
Immune system disorders: angioedema, hypersensitivity
Metabolism and nutrition disorders: hypoglycemia
Musculoskeletal and connective tissue disorders: arthropathy
Nervous system disorders: cerebrovascular accident, syncope, paresthesia
Psychiatric disorders: insomnia, amnesia, nightmares
Reproductive system and breast disorders: sexual dysfunction
Skin and subcutaneous tissue disorders: urticaria, psoriasis, rash, alopecia
Vascular disorders: Raynaud's phenomenon

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No data are available in regard to overdosage in humans.

The most common signs and symptoms to be expected with overdosage with administration of a systemic beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure.

The following therapeutic measures should be considered:

(1) Gastric lavage: if ingested.
(2) Symptomatic bradycardia: use atropine sulfate intravenously in a dosage of 0.25 mg 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.
(3) 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.
(4) Bronchospasm: use isoproterenol hydrochloride. 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 intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.
(6) Heart block (second or third degree): use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

T-LO

The recommended starting dosage is one drop of 0.25% solution in the affected eye(s) twice a day.

If clinical response is not adequate, the dosage may be changed to one drop of 0.5% solution in each affected eye(s) twice a day. If the patient's intraocular pressure (IOP) is still not at a satisfactory level on this regimen, concomitant therapy with miotics, epinephrine and systemically administered carbonic anhydrase inhibitors may be instituted with T-LO. Other topically applied medications should be administered at interval of not less than 10 minutes.

Since in some patients the IOP-lowering response to T-LO Solution may require a few weeks to stabilize, evaluation should include a determination of IOP after approximately 4 weeks of treatment with T-LO.

If IOP is maintained at satisfactory levels, the dosage schedule may be changed to one drop a day in the affected eye(s). Because of naturally occurring diurnal variations in IOP, satisfactory response to the once-a-day dose is best determined by measuring IOP at different times during the 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 T-LO started on the following day with 1 drop of 0.25% T-LO in the affected eye(s) twice a day. The dose may be increased to 1 drop of 0.5% T-LO twice a day if the clinical response is not adequate.

When a patient is transferred from a single anti-glaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent already being used and add one drop of 0.25% T-LO in each affected eye(s) twice a day. On the following day, discontinue the previously used anti-glaucoma agent completely and continue with T-LO. If a higher dosage of T-LO is required, substitute one drop of 0.5% solution in each affected eye(s) twice a day.

When a patient is transferred from several concomitantly administered anti-glaucoma agents, individualization is required. The physician may be able to discontinue some or all of the other anti-glaucoma agents. Adjustments should involve one agent at a time.

TIMOLOL MALEATE-EX

The usual starting dose is one drop of 0.25% 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% in the affected eye(s) once a day.

If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with miotics, epinephrine and systemically administered carbonic anhydrase inhibitors may be instituted with TIMOLOL MALEATE-EX. Other topically applied medications should be administered at intervals of not less than 10 minutes.

When a patient is transferred from T-LO to TIMOLOL MALEATE-EX, the solution should be discontinued after proper dosing on one day, and treatment with the same concentration of TIMOLOL MALEATE-EX 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 TIMOLOL MALEATE-EX started on the following day with 1 drop of 0.25% TIMOLOL MALEATE-EX in the affected eye(s) once a day. The dose may be increased to 1 drop of 0.5% TIMOLOL MALEATE-EX once a day if the clinical response is not adequate.

When a patient is transferred from a single anti-glaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent already being used and add one drop of 0.25% TIMOLOL MALEATE-EX in each affected eye(s) once a day. On the following day, discontinue the previously used anti-glaucoma agent completely and continue with TIMOLOL MALEATE-EX. If a higher dosage of TIMOLOL MALEATE-EX is required, substitute one drop of 0.5% solution in each affected eye(s) once a day.

Nasolacrimal occlusion or gently closing the eyelid for 2 minutes after instillation (of either T-LO or TIMOLOL MALEATE-EX) is recommended. This may reduce the systemic absorption of medications administered via the ocular route and result in a decrease in systemic adverse events.

To avoid contamination, patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. The contents should not be used for more than one month after the date on which the container is first opened.

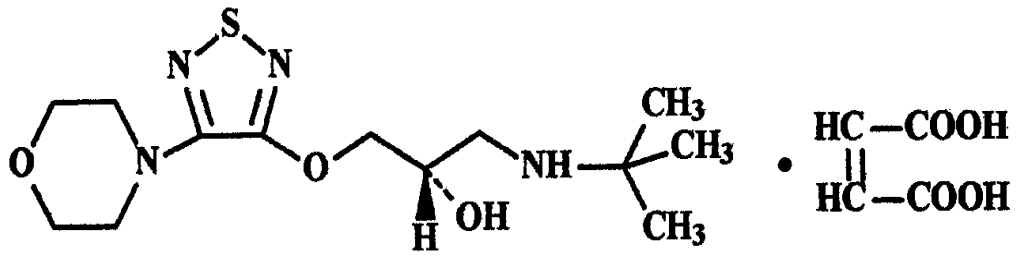
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Timolol Maleate

Chemical Name: (-)-1-(tert-butyl amino)-3-[(4-morpholino)-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1:1) salt

Structural Formula:



Molecular Formula: $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

Molecular Weight: 432.49

Melting Point: 201.5 - 202.5°C

pKa: 9.2

pH: approximately 4 in a 2% aqueous solution

Physical Description: White, odourless, crystalline powder which is soluble in water, methanol, and alcohol.

Composition:
T-LO is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths: 0.25% and 0.5%.
Medicinal Ingredient: Each mL of T-LO 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of T-LO 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate).
Preservative: Benzalkonium chloride 0.01%.
Non-medicinal ingredients: monobasic and dibasic sodium phosphate, sodium hydroxide and/or hydrochloric acid to adjust pH, and purified water.

TIMOLOL MALEATE-EX is supplied as a sterile, isotonic buffered, aqueous solution of timolol maleate in two dosage strengths: 0.25% and 0.5%.
Medicinal ingredient: Each mL of TIMOLOL MALEATE-EX 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of TIMOLOL MALEATE-EX 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate).
Preservative: Benzododecinium bromide 0.012%.
Non-medicinal ingredients: xanthan gum, mannitol, boric acid, tromethamine, polysorbate 80, purified water.

Stability and Storage Recommendations:
Protect from light. Keep out of the reach and sight of children.

T-LO: Store at room temperature (15°C - 30°C).

TIMOLOL MALEATE-EX: Store at 4 °C - 30°C .

The contents of T-LO and TIMOLOL MALEATE-EX should not be used for more than one month after the date on which the container is first opened.

AVAILABILITY OF DOSAGE FORMS

T-LO is a sterile, clear, colourless to pale yellow solution. T-LO, 0.5%, is supplied in 5 mL and 10 mL white, opaque, plastic ophthalmic DROP-TAINER* dispensers with a controlled drop tip, and the 0.25% is supplied in 10 mL.

TIMOLOL MALEATE-EX is a sterile, colourless to pale yellow, clear to slightly translucent, and slightly viscous solution. TIMOLOL MALEATE-EX, 0.25% or 0.5%, is supplied in 5 mL white, opaque, plastic ophthalmic DROP-TAINER* dispensers with a controlled drop tip.

PHARMACOLOGY

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.

T-LO and TIMOLOL MALEATE-EX, when applied topically in the eye, have the action of reducing elevated as well as normal intraocular pressure (IOP), whether or not associated with glaucoma. Elevated IOP is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in IOP following administration of T-LO can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours. Significant lowering of IOP has been maintained for periods as long as 24 hours with T-LO one drop b.i.d and TIMOLOL MALEATE-EX once daily. Repeated observations indicate that the IOP-lowering effect of T-LO and TIMOLOL MALEATE-EX is well maintained over study periods of three years and one year, respectively.

The precise mechanism of the ocular hypotensive action of T-LO is not clearly established at this time. Tonography and fluorophotometry studies in man suggest 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, T-LO and TIMOLOL MALEATE-EX reduces IOP with little or no effect on accommodation or pupil size. These 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.

In clinical studies, T-LO and TIMOLOL MALEATE-EX were generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine.

As with the use of other anti-glaucoma drugs, diminished responsiveness to T-LO after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean IOP has been observed after initial stabilization. In a long-term clinical trial of 157 patients, TIMOLOL MALEATE-EX 0.5% once daily maintained IOP reductions over the one year study period.

T-LO has also been used in patients with glaucoma wearing conventional (polymethylmethacrylate) hard contact lenses, and has generally been well tolerated. T-LO has not been studied in patients wearing lenses made with materials other than polymethylmethacrylate.

In controlled, double-masked, multicenter clinical studies, TIMOLOL MALEATE-EX administered once daily was shown to be equally effective in lowering IOP as the equivalent concentration of TIMOPTIC® (timolol maleate solution) administered twice daily and TIMOPTIC-XE® once daily. The effect of timolol in lowering IOP was evident for 24 hours with a single dose of TIMOLOL MALEATE-EX. Repeated observations over a twelve month study period indicate that the IOP-lowering effect of TIMOLOL MALEATE-EX was consistent.

TIMOLOL MALEATE-EX administered once daily had a safety profile similar to that of an equivalent concentration of TIMOPTIC® administered twice daily and TIMOPTIC-XE® once daily. Due to the physical characteristics of the formulation, transient blurred vision was reported in patients administered TIMOLOL MALEATE-EX.

TIMOLOL MALEATE-EX has not been studied in patients wearing contact lenses.

TOXICOLOGY

Ocular Effects
No adverse ocular effects were observed in rabbits and dogs administered Timolol Maleate Ophthalmic Solution topically in studies lasting one and two years respectively.

Acute Toxicity (LD_{50})

Species and Age	Sex	Route of Administration	LD_{50} (mg/kg)
Mouse (A)	F	Oral	1 190
	F	Intravenous	222
	F	Subcutaneous	1 040
Rat (YA)	M	Oral	947
	F	Oral	900
	M	Oral (fed)	1 800
	M	Intraperitoneal	390
	F	Intraperitoneal	383
Rat (W)	M	Oral	1 040
	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 Interaction 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 effect on the toxicity of timolol maleate. Timolol maleate had no effect on hypoprothrombinemia induced by bishydroxycoumarin in the dog.

Subacute Toxicity
In rats treated with 100 to 400 mg/kg for seven weeks, excessive salivation seen 5 to 10 minutes after dosing has 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 ptylamism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg 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 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.

Carcinogenicity

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 in 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/day basis). Timolol caused dose-related elevations of serum prolactin in female mice at doses of 100 mg/kg or more, but only very slight transient elevations were found in male mice at does of 500 mg/kg. Since numerous studies have demonstrated that drugs which cause elevations if serum prolactin are associated with mammary tumours in rodents, the mammary tumours 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.

Mutagenicity

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse and the Micronucleus test and Ctyogenic assay (dose up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the high test concentrations of timolol employed, 5 000 or 10 000 μg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA 100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA 100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion of a positive Ames Test.

Reproduction and Teratology
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.

TIMOLOL MALEATE-EX contains xanthan gum at concentrations up to 0.6%. The oral LD_{50} value for xanthan gum is greater than 5 g/kg in rats. Xanthan gum was not classified as an ocular irritant when a single 0.2 mL dose of a 1% xanthan gum solution was administered to rabbit eyes. Xanthan gum did not elicit any dermal responses when a skin sensitization assay was conducted in guinea pigs. In addition, oral administration (in feed) of up to 1 g/kg/day of xanthan gum for two years to rats and dogs did not elicit any treatment-related changes in hematology parameters or histopathology. Likewise, no deaths were observed in either study.

In rabbits treated twice daily for three months with topical ocular administration of TIMOLOL MALEATE-EX 0.5%, ocular effects were minimal in nature, confined to the conjunctiva, comparable to the ocular findings observed in the vehicle control group and the TIMOPTIC-XE® group, and judged to be of no clinical significance.

Results from a one year study of primates treated twice daily with topical ocular administration of TIMOLOL MALEATE-EX 0.5% demonstrated that there were no treatment-related findings with regard to clinical signs, body weight difference, biomicroscopic observations of eyes, indirect ophthalmoscopic evaluations, pachymetry measurements, specular microscopy and clinical pathology.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr T-LO
Timolol Ophthalmic Solution (0.25%, 0.5% w/v)

Pr TIMOLOL MALEATE-EX
Timolol Ophthalmic Gel Forming Solution (0.25%, 0.5% w/v)

Read this carefully before you start taking **T-LO** or **TIMOLOL MALEATE-EX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **T-LO** or **TIMOLOL MALEATE-EX**.
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 is T-LO and TIMOLOL MALEATE-EX used for?
T-LO and TIMOLOL MALEATE-EX are prescription eyes medications. They are used to lower high eye pressure in adults with glaucoma or other eyes diseases (e.g., ocular hypertension).

How does T-LO and TIMOLOL MALEATE-EX work?
T-LO and TIMOLOL MALEATE-EX are brand names. Both T-LO and TIMOLOL MALEATE-EX contains the active ingredient timolol maleate. Timolol maleate belong to a class of medication called beta-blockers. It lowers eye pressure by causing the eye to make less fluid.

What are the ingredients in T-LO?
Medicinal ingredients:
T-LO contains the active ingredient timolol maleate. It is available in the following two strengths:

- T-LO 0.25% - each mL contains 2.5 mg of timolol (as timolol maleate).
- T-LO 0.5% - each mL contains 5.0 mg of timolol (as timolol maleate).

Non-medicinal ingredients: Benzalkonium chloride 0.01% (preservative), monobasic and dibasic sodium phosphate, sodium hydroxide and/or hydrochloric acid to adjust pH, and purified water.

What are the ingredients in TIMOLOL MALEATE-EX?

Medicinal ingredient:
TIMOLOL MALEATE-EX contains the active ingredient timolol maleate. It is available in the following two strengths:

- TIMOLOL MALEATE-EX 0.25% - each mL contains 2.5 mg of timolol (as timolol maleate).

- TIMOLOL MALEATE-EX 0.5% - each mL contains 5.0 mg of timolol (as timolol maleate).

Non-medicinal ingredients: Benzododecinium bromide 0.012% (preservative), xanthan gum, mannitol, boric acid, tromethamine, polysorbate 80, purified water.

T-LO and TIMOLOL MALEATE-EX come in the following dosage forms:
T-LO, 0.5% or 0.25% comes as a solution (liquid) to use as eye drops.

T-LO, 0.5% is supplied in 5 mL and 10 mL bottle designed to deliver a precise quantity of the medication. T-LO, 0.25% is supplied in a similar 10mL bottle.

TIMOLOL MALEATE-EX, 0.25% or 0.5% comes as a gel-forming solution (a liquid that thickens to a gel when instilled in the eye) to use as eye drops. It is supplied in 5 mL bottle designed to deliver a precise quantity of the medication.

Do not use T-LO and TIMOLOL MALEATE-EX:
- if you are allergic to:
    - timolol or any ingredient in T-LO or TIMOLOL MALEATE-EX (see What are the ingredients in T-LO or TIMOLOL MALEATE-EX?).
    - if you are allergic to any other beta-blockers such as atenolol, betaxolol, labetalol, levobunolol, metoprolol, nadolol, propranolol, sotalol.
- if you have or have had lung diseases or breathing problems such as asthma, chronic obstructive pulmonary disease (COPD).
- if you suffer from certain heart disease, such as a slow heart rate, an irregular heartbeat, or heart failure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take T-LO or TIMOLOL MALEATE-EX. Talk about any health conditions or problems you may have, including if you:
- have or have had diabetes or other blood sugar problems. Timolol may mask signs of low blood sugar;
- have or have had thyroid problems;
- have or have had diseases that causes weakness in your muscles. Beta-blockers have been reported to increase muscle weakness in some patients;
- have or have had heart diseases such as:
    - coronary heart disease (narrowing of the small blood vessels that supply blood and oxygen to the heart causing chest pain or discomfort when you do certain activities);
    - heart failure (weak heart);
    - low blood pressure, heartbeat that is not normal, or a very slow heartbeat.
- have or have had lung or breathing problems (e.g., asthma, chronic obstructive lung disease);
- have or have had blood circulation problems such as Raynaud's syndrome;

- have allergic problems such as eczema, hives or hay fever;
- have allergies to any other medications, foods or any other substances such as preservatives or dyes;
- wear contact lenses. TIMOLOL MALEATE-EX has not been studied in people wearing contact lenses (see "Other warnings you should know about section" below);
- are already using another beta-blocker eye drop. It is not recommended to use two beta-blocker eye drops at the same time;
- have or have had eye problems;
- are pregnant or planning to become pregnant;
- are breast feeding or planning to breast feed.

Other warnings you should know about:

While you are using T-LO and TIMOLOL MALEATE-EX

- **Driving and using machines**: T-LO and TIMOLOL MALEATE-EX may cause temporary blurred vision after using the drops. Make sure that your vision is clear before driving a car or operating machinery.
- **If you wear contact lenses:**
    - T-LO contains a preservative (benzalkonium chloride) which may cause eye irritation and discolour soft contact lenses. If you wear contact lenses, remove them before using T-LO. Wait at least 15 minutes after using T-LO to put your lenses back in.
    - TIMOLOL MALEATE-EX contains a preservative (benzododecinium chloride) that may be absorbed by contact lenses.
- **If you are planning a surgery**. Timolol may change effects of some medicines used during anaesthesia. Anaesthesia is a treatment with certain medicines so that you do not feel pain during surgery.
- If you have an eye injury, or develop an eye infection while using T-LO eye drops, tell your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with T-LO or TIMOLOL MALEATE-EX:
- Adrenaline (epinephrine) (used to treat life-threatening allergic reactions).
- A group of medicines called oral calcium channel blockers such as diltiazem,verapamil.
- A group of medicines called Catecholamine-depleting drugs (e.g. reserpine).
- Beta-adrenergic blocking agents commonly referred to as beta-blockers such as atenolol, labetalol, metoprolol, nadolol, propranolol, sotalol.
- Medications used to treat certain type of abnormal heart rhythm such as amiodarone, digoxin, quinidine.
- Clonidine (a medication used to treat high blood pressure). Do not stop taking clonidine

without talking to your healthcare professional.
- Cimetidine (a medication used to treat stomach problem), Fluoxetine and paroxetine [both medications are used to treat depression (low blood mood)]. Ask your healthcare professional if you are not sure if any of your medicines are listed above.

This is not a list of all drugs that interact with T-LO or TIMOLOL MALEATE-EX.

Always keep a list of your medicines and show it to your healthcare professional when you get a new medicine. It is important that your healthcare professional reviews all medications and supplements you are taking before prescribing T-LO or TIMOLOL MALEATE-EX.

How to take T-LO and TIMOLOL MALEATE-EX:

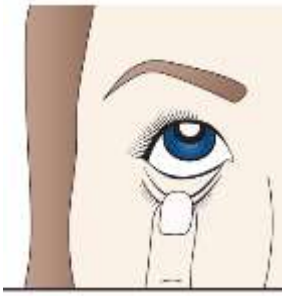
1- Wash your hands before use. Remove contact lenses before using eye drops.

2- Twist the cap off, being careful not to touch the dropper tip.

3- Hold the bottle between the thumb and middle finger.

4- Tilt head back.

5- Pull the lower eyelid down to form a pocket below the eye.



6- Gently press on the base of the bottle to release one drop. Do not squeeze the bottle.

7- Close the eye for 2 or 3 minutes. If a drop misses the eye, try again.

8- Repeat steps 3 to 7 for the other eye if required.

9- After use, immediately put the cap back on the bottle and keep tightly closed when not in use.

- Be careful not to touch the dropper tip against your eye, eyelid or anything else to avoid contaminating the eye drops.
- If you are using another eye medication, use it at least 10 minutes before or after you use T-LO or TIMOLOL MALEATE-EX.

Usual dose:

- **For T-LO**: Instill one drop in the affected eye(s) twice a day.
- **For TIMOLOL MALEATE-EX**: Instill one drop in the affected eye(s) once a day.

Follow the directions on your prescription label carefully, and ask your healthcare professional to

explain any part you do not understand.

Use T-LO or TIMOLOL MALEATE-EX exactly as directed. Do not start, stop, or change the dose of any drug without checking with your healthcare professional.

Overdose:
If you use too many drops, you may feel light-headed or dizzy, you may faint, have a very slow pulse rate, or have wheezing or difficulty breathing.

If you or someone accidently swallow T-LO or TIMOLOL MALEATE-EX or if you use too much drops, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Use T-LO or TIMOLOL MALEATE-EX at the same time of day. 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.

What are possible side effects from using T-LO or TIMOLOL MALEATE-EX?

- Stomach or bowel problems:
  - Nausea and vomiting
  - Dry mouth
  - Discomfort in the upper belly or abdomen
  - Change in taste
- Problems with your eye/s such as:
  - Blurred vision
  - Burning and stinging
  - Dry eyes
  - Pain in the eye
  - Conjunctivitis (pink eye)
  - Itching and redness of the eye
  - Feeling of having something in the eye,
  - Bleparitis (eyelids problem with signs such as irritated, itchy, reddened and swollen eyelids with dandruff-like debris builds up at the base of the eyelashes)
  - Visual changes (e.g. double visions)
  - Watery eyes
- Changes in the way your hands and feet feel such as:
  - Raynaud's phenomenon
    - cold fingers or toes
    - colour change in (white, blue then red) in fingers when exposed to the cold or stress
    - numbness or tingling in the fingers or toes

- Paresthesia : abnormal sensation such as burning or prickling sensation that is usually felt in the hands or feet, but can also occur in other parts of the body
- Difficulty thinking or working because of:
    - Headache
    - Tiredness, weakness
    - Difficulty sleeping, nightmares
    - Changes in mood such as depression, memory loss
- Hair loss or thinning
- Less desire for sex
- Skin rash

Call your healthcare professional or get medical help if any of the side effects listed above bother you or do not go away.

These are not all the possible side effects you may feel when taking T-LO or TIMOLOL MALEATE-EX. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
dizziness and light-headedness, which may be due to low blood pressure		√	
swelling of the hands, feet, ankles or legs		√	
Breathing problems: • wheezing, difficulty in breathing • shortness of breath			√
Heart problems: • feelings that your heart is skipping a beat or beating too hard or too fast Raynaud's phenomenon palpitations) • feeling dizzy or confused,			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug
• have trouble breathing, • think you may faint, • have pain or tightness in your chest			
Allergic reactions: • swelling of the face, lips, mouth, tongue or and throat which may cause difficulty in breathing or swallowing • wheezing, difficulty in breathing,shortness of breath • hives, severe itching and rash			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

How do to store and/or throw out T-LO or TIMOLOL MALEATE-EX:

- Keep T-LO and TIMOLOL MALEATE-EX:
  - away from direct light.
  - out of the reach and sight of children.
- T-LO: Store at room temperature (15°C - 30°C).
- TIMOLOL MALEATE-EX: Store at 4 °C - 30°C.
- Write the date on the bottle when you open the eye drops and throw out any remaining solution one month after opening the bottle. The best way to dispose of your medication

is through a medicine take-back program. Check with your pharmacist about how to throw out unused medicines.
- Do not use T-LO and TIMOLOL MALEATE-EX after the expiry date on the bottle.

If you want more information about T-LO and TIMOLOL MALEATE-EX:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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