

**PRODUCT MONOGRAPH**

<sup>Pr</sup> **APO-TIMOP GEL**  
**timolol maleate ophthalmic gel forming solution**

**0.25%, 0.5% w/v**

**Sterile Ophthalmic Solution**

**Elevated intraocular pressure therapy**

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**Pr APO-TIMOP GEL**

**timolol maleate ophthalmic gel forming solution**

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form/ Strength</b>	<b>Clinically Relevant Non-medicinal Ingredients</b>
Ophthalmic	Solution/ 0.25% and 0.5%	Benzododecinium Bromide (as preservative), gellan gum, mannitol, tromethamine and water for injection.

**INDICATIONS AND CLINICAL USE**

APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) is indicated for the reduction of elevated intraocular pressure.

In clinical trials timolol maleate ophthalmic gel forming solution 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**

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

## **WARNINGS AND PRECAUTIONS**

### **General**

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

### **Cardiovascular**

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered.

Cardiac failure should be adequately controlled before beginning therapy with timolol maleate ophthalmic gel forming solution. Patient with a history of cardiovascular disease, including cardiac failure, should be watched for signs of deterioration of these diseases, and pulse rates should be monitored.

Due to its negative effect on conduction time, beta blockers should only be given with caution to patients with first degree heart block.

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 solution, USP. These are also potential complications of therapy with timolol maleate ophthalmic gel forming solution.

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 timolol maleate ophthalmic gel forming solution, alternative therapy should be considered.

Patients with severe peripheral circulatory disturbance/disorders (e.g. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

### **Endocrine and Metabolism**

#### **Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus**

Timolol maleate ophthalmic gel forming solution 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.

#### **Masking of 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.

### **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 unresponsive 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**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 Timolol maleate ophthalmic gel forming solution is used to reduce elevated intraocular pressure in angle-closure glaucoma they should be used with a miotic and not alone.

#### **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 APO-TIMOP GEL (timolol maleate ophthalmic solution, USP) after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least 3 years, no significant difference in mean intra ocular pressure has been observed after initial stabilization.

#### **Contact Lenses**

The preservative in APO-TIMPO GEL is benzododecinium bromide. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. For timolol maleate ophthalmic gel forming solution, studies have not been done in patients wearing contact lenses. However, in a clinical study, the time required to eliminate 50% of the gel forming solution from the eye was up to 30 minutes.

### **Neurologic**

#### **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.

## **Peri-Operative Considerations**

### **Major Surgery**

The necessity or desirability of withdrawal of  $\beta$ -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.

$\beta$ -blocking ophthalmological preparations may block systemic  $\beta$ -agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving APO-TIMOP GEL.

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  $\beta$ -adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

### **Respiratory**

In patients with mild/moderate chronic obstructive pulmonary disease (COPD), Timolol maleate ophthalmic gel forming solution should be used with caution, and only if the potential benefit outweighs the potential risk.

### **Special Populations**

#### **Pregnant Women**

Timolol maleate ophthalmic gel forming solution has not been studied in human pregnancy. The use of timolol maleate ophthalmic gel forming solution requires that the anticipated benefit be weighed against possible hazards. 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.

#### **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.*

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

Like other topically applied ophthalmic drugs, Timolol maleate ophthalmic gel forming solution is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic betablocking agents. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

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

### **Ocular**

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

The adverse reactions reported for APO-TIMOP (timolol maleate ophthalmic solution, USP) are potential adverse reactions for APO-TIMOP GEL. Please refer to the list below.

### **Body as a Whole**

Headache, asthenia, fatigue.

### **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, chest pain, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, palpitation, atrioventricular block, cardiac arrest, cardiac failure, 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**

Dysgeusia, nausea, diarrhea, dyspepsia, dry mouth, abdominal pain, vomiting.

### **Hypersensitivity**

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

### **Immunologic**

Systemic lupus erythematosus.

**Integumentary**

Alopecia, psoriasisiform rash or exacerbation of psoriasis.

**Metabolism and nutrition disorders**

Hypoglycemia.

**Musculoskeletal**

Myalgia.

**Nervous System/Psychiatric**

Depression, insomnia, nightmares, memory loss, increases in signs and symptoms of myasthenia gravis, dizziness, 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 itching, tearing, redness conjunctivitis, conjunctival injection, blepharitis, keratitis, blurred vision, decreased corneal sensitivity, and dry eyes. Visual disturbances: including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, corneal erosion ptosis, and choroidal detachment following filtration surgery (see WARNINGS AND PRECAUTIONS), tinnitus.

**Urogenital**

Decreased libido, Peyronie's disease, sexual dysfunction.

**Causal Relationship Unknown**

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

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

**DRUG INTERACTIONS****Drug-Drug Interactions****Beta-Adrenergic Blockers**

Patients who are already receiving a beta blocker systemically and who are given APO-TIMOP GEL 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 APO-TIMOP GEL is administered together with an oral calcium channel blocker or beta- adrenergic blocking agents, catecholamine-depleting drugs such as reserpine, antiarrhythmics, digitalis glycosides, parasympathomimetics or guanethidine.

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

The potential for mydriasis also exists from concomitant therapy with APO-TIMOP GEL and epinephrine.

### **Quinidine**

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

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

#### **Clinical Laboratory Test**

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

No specific drug interaction studies have been performed with Timolol maleate ophthalmic gel forming solution.

## **DOSAGE AND ADMINISTRATION**

### **Recommended Dose and Dosage Adjustment**

The usual starting dosage is one drop of 0.25% APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) 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% APO-TIMOP GEL 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 APO-TIMOP GEL. Other topically applied medications should be administered no less than 10 minutes before APO-TIMOP GEL.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in an increase in local activity.

### **How to Transfer Patients from Other Therapy**

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

When a patient is transferred from a single antiglaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent and add one drop of 0.25% APO-TIMOP GEL to each affected eye once a day. On the following day, discontinue the previously used antiglaucoma agent and continue 0.25% APO-TIMOP GEL. If a greater response is required, substitute one drop of 0.5% APO-TIMOP GEL for the 0.25% dosage.

### **Missed Dose**

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

## **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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There have been reports of inadvertent overdose with APO-TIMOP (timolol maleate ophthalmic solution USP) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

The following additional therapeutic measures should be considered:

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

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

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

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

**Acute cardiac failure:** Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.

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

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Timolol maleate is a general beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

### **Pharmacokinetics**

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

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice-daily topical administration of timolol maleate ophthalmic solution

0.5% for 8 days. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

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

## **STORAGE AND STABILITY**

Store at room temperature 15°C to 30°C. Protect from light and freezing. Discard 28 days after the container is first opened.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) is a sterile, colourless to nearly colourless, slightly opalescent, slightly viscous, aqueous ophthalmic solution.

### **Composition**

Each mL of APO-TIMOP GEL 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of APO-TIMOP GEL 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate). Non-medicinal ingredients: 0.012% benzododecinium bromide (as preservative), gellan gum, mannitol, tromethamine and water for injection.

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 APO-TIMOP GEL contacts the pre-corneal tear film, it becomes a gel. The vehicle of APO-TIMOP GEL, gellan gum, increases the contact time of the drug with the eye.

### **Packaging**

APO-TIMOP GEL 0.25%, equivalent to 2.5 mg timolol per mL; is supplied in a 11 mL white opaque, low-density polyethylene ophthalmic dispenser bottle and white translucent LDPE dropper tip and a light blue opaque HDPE cap with sealing tape. Each bottle contains 5 mL of APO-TIMOP GEL.

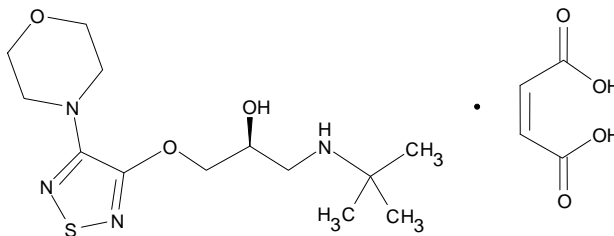
APO-TIMOP GEL 0.5%, equivalent to 5.0 mg timolol per mL; is supplied in a 11 mL white opaque, low-density polyethylene ophthalmic dispenser bottle and white translucent LDPE dropper tip and a light yellow opaque HDPE cap with sealing tape. Each bottle contains 5 mL of APO-TIMOP GEL.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

<b>Proper name:</b>	Timolol maleate
<b>Chemical name:</b>	(-)-1-(tert-butylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yl)oxy-2-propanol maleate (1:1)
<b>Molecular formula:</b>	$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$
<b>Molecular mass:</b>	432.49 g/mol
<b>Structural formula:</b>	



#### Physicochemical Properties:

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

### CLINICAL TRIALS

Clinical studies have shown that the intraocular pressure lowering effect of timolol maleate ophthalmic gel forming solution administered once a day is equivalent to timolol maleate ophthalmic solution administered twice a day. The vehicle of timolol maleate ophthalmic gel forming solution increases the contact time of the drug with the eye.

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

Timolol maleate ophthalmic gel forming solution has not been studied in patients wearing contact lenses.

In a clinical study, the time required to eliminate 50% of the gel forming solution from the eye was up to 30 minutes (see WARNINGS AND PRECAUTIONS).

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

There was a higher incidence of transient blurred vision following instillation in patients administered timolol maleate ophthalmic gel forming solution.

## **DETAILED PHARMACOLOGY**

APO-TIMOP GEL (timolol maleate ophthalmic solution, USP) reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

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

No adverse ocular effects were observed in rabbits and monkeys administered timolol maleate ophthalmic gel forming solution topically in studies lasting one month and 12 months, respectively.

**Table 1: 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.

The oral LD<sub>50</sub> of gellan gum is greater than 5000 mg/kg in rats.

### **Oral Interactions Studies**

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

### **Subacute Toxicity**

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

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

### **Chronic Toxicity**

#### **Rats**

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

#### **Dogs**

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

### **Tumorigenic Tests**

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



association between serum prolactin and mammary carcinoma has been established.

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

### **Reproductive Studies**

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

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### PART III: CONSUMER INFORMATION

<sup>Pr</sup> APO-TIMOP GEL

timolol maleate ophthalmic gel forming solution

This leaflet is Part III of a three-part “Product Monograph” published when APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-TIMOP GEL. Contact your physician or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### **What the medication is used for:**

APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) 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 APO-TIMOP GEL if you:

- are allergic to any of its components (see What the nonmedicinal ingredients are section below);
- have now or have had in the past certain serious breathing problems such as asthma
- have chronic obstructive lung disease
- have certain heart diseases or conditions (such as slow or irregular heartbeats);
- are breast feeding or intend to breast feed

##### **What the medicinal ingredient is:**

Timolol maleate

##### **What the important nonmedicinal ingredients are:**

Benzododecinium bromide (as preservative), gellan gum, mannitol, tromethamine and water for injection.

##### **What dosage forms it comes in:**

APO-TIMOP GEL 0.25% is an eye drop provided in a white plastic dropper bottle with a light blue cap. APO-TIMOP GEL 0.5% is provided in a white plastic dropper bottle with a light yellow cap. Each bottle

contains 5 mL of solution in an 11 mL bottle.

#### 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
- APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) contains the preservative benzododecinium bromide. If you wear contact lenses, you should consult your physician or pharmacist before using APO-TIMOP GEL. 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 have now or have had in the past, heart problems (such as coronary heart disease, heart failure or low blood pressure).
- If you have now or have had in the past, heart rate disturbances (such as slow or irregular heartbeats).
- If you have or have had in the past, poor blood circulation problems (such as Raynaud’s syndrome).
- If you have or have had in the past, lung or breathing problems (such as asthma or chronic obstructive lung disease).
- If you have or have had in the past, diabetes or other blood sugar problems.
- If you are planning major surgery, including eye surgery, as using APO-TIMOP GEL may change the effects of some medicines during anaesthesia.
- 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.

**APO-TIMOP GEL IS NOT RECOMMENDED FOR USE IN 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, diabetes or depression including beta-blockers such as atenolol,

epinephrine, quinidine, calcium channel blockers or catecholamine depleting drugs such as reserpine. No specific drug interaction studies have been done for APO-TIMOP GEL.

**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 APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) is causing an allergic reaction (for example, skin rash or itching), stop its use and contact your physician as soon as possible.
- If you develop any eye irritation or any new eye problems such as redness of the eye or swelling of the eyelids, contact your physician immediately.
- If you are using APO-TIMOP GEL with another eyedrop, the drops should be instilled at least 10 minutes apart.
- Do not change the dosage recommended by your physician. If you must stop treatment, contact your physician immediately.
- Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.
- Contact your physician without delay if you have ocular surgery or develop a condition that was not present at the time this medication was prescribed (e.g., trauma, an infection, etc.).
- The contents of the container should not be used for more than one month after the date on which the container is first opened.

**Usual Adult Dose:**

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

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

**Overdose:**

If you think you have taken too much APO-TIMOP GEL, contact your healthcare professional, hospital emergency department or regional Poison Control

Centre immediately, even if there are no symptoms.

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

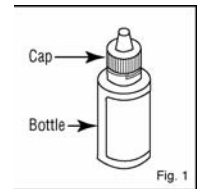
In the event of overdose, contact your doctor, hospital emergency department or regional Poison Control Centre.

**Missed Dose:**

It is important to apply APO-TIMOP GEL 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 white plastic sealing tape between the bottle and cap is unbroken (Fig. 1).



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

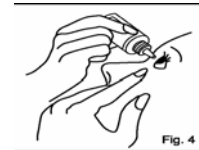
3. To break the seal and open the bottle, unscrew the cap by turning as indicated by the arrow (Fig. 2).



4. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye (Fig. 3).



5. Invert the bottle, and press the side of the bottle lightly (as shown in Fig. 4) until a single drop is dispensed into the eye as directed by your physician.



**DO NOT TOUCH YOUR EYE OR EYE-LID 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.
- Repeat steps 4 & 5 with the other eye if instructed to do so by your physician.
  - The dispenser tip is designed to provide a pre-measured drop; therefore, do NOT enlarge the hole of the dispenser tip.
  - After you have used all doses, there will be some APO-TIMOP GEL left in the bottle. You should not be concerned since an extra amount of APO-TIMOP GEL has been added and you will get the full amount of APO-TIMOP GEL that your physician prescribed. Do not attempt to remove excess medicine from the bottle.
  - Tell your physician if you wear contact lenses. Depending on the type of lens, your physician may advise that you re-insert your contact lenses not earlier than 15 minutes after application of APO-TIMOP GEL.

**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 muscle pain; abdominal pain; nausea; vomiting symptoms such as itching, burning and stinging, dry eyes, redness of the eye, foreign body sensation or visual changes, such as double vision.
- Other side effects may also occur rarely, and some of these may be serious. These may include shortness of breath.
- Timolol has been reported rarely to increase muscle weakness in some patients with 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.

Your vision may be temporarily blurred for 30 seconds to 5 minutes immediately after putting APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) in your eye. Make sure that your vision is clear before you drive a motor vehicle or operate machinery.

Serious side effects and what to do about them				
Symptom/effect	Uncommon	Only if severe	In all cases	Stop taking drug and get immediate medical help
Slow heartbeat				✓

n				
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 APO-TIMOP GEL, contact your physician or pharmacist.*

**HOW TO STORE IT**

Store at room temperature 15°C to 30°C. Protect from light and freezing. Discard 28 days after opening.

The expiry date for APO-TIMOP GEL (timolol maleate ophthalmic gel forming solution) is printed on the package. Do not use the medicine in the package after this date.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

**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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) 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.*

**MORE INFORMATION**

**If you want more information about APO-TIMOP GEL:**

- 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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <http://www.apotex.ca/products>, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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