

PRODUCT MONOGRAPH

Pr_{pms}-TIMOLOL

Timolol Maleate Ophthalmic Solution USP

0.25% and 0.5%

Sterile Ophthalmic Solution

Elevated Intraocular Pressure Therapy

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Pr
pms-TIMOLOL
Timolol maleate
Ophthalmic Solution USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

pms-TIMOLOL (timolol maleate ophthalmic solution) is indicated for the reduction of elevated intraocular pressure:

In clinical trials timolol maleate ophthalmic 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

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

WARNINGS AND PRECAUTIONS

General

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

Timolol maleate ophthalmic 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.

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

Cardiac failure should be adequately controlled before beginning therapy with timolol maleate ophthalmic solution. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solutions.

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

Endocrine and Metabolism

Thyrotoxicosis

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

Immune

Risk from Anaphylactic Reaction

While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens, either accidental, diagnostic, or therapeutic. These patients may be more resistant to treatment of

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

Ophthalmologic

Choroidal Detachment

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

As with the use of other antiglaucoma drugs, diminished responsiveness to timolol maleate ophthalmic solution 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 pms-TIMOLOL ophthalmic solution is benzalkonium chloride. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. Therefore, pms-TIMOLOL ophthalmic solution should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

Neurologic

Muscle Weakness

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

Peri-Operative Considerations

Major Surgery

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

Special Populations

Pregnant Women:

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

Nursing Women:

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics:

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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

Timolol maleate ophthalmic solution is usually well tolerated.

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

Body as a Whole

Headache, asthenia, fatigue, chest pain.

Cardiovascular

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

Digestive

Nausea, diarrhea, dyspepsia, dry mouth.

Hypersensitivity

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

Immunologic

Systemic lupus erythematosus.

Integumentary

Alopecia, psoriasiform rash or exacerbation of psoriasis.

Nervous System/Psychiatric

Dizziness, depression, insomnia, nightmares, memory loss, increase in signs and symptoms of myasthenia gravis, paresthesia.

Respiratory

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

Special Senses

Signs and symptoms of ocular irritation: including burning and stinging, conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity, and dry eyes.

Visual disturbances: including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, and choroidal detachment following filtration surgery (see WARNINGS AND PRECAUTIONS).

Tinnitus.

Urogenital

Decreased libido, Peyronie's disease.

Causal Relationship Unknown

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

Potential Adverse Reactions

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

DRUG INTERACTIONS

Drug-Drug Interactions

Beta-adrenergic Blockers

Patients who are already receiving a beta blocker systemically and who are given timolol maleate ophthalmic 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 timolol maleate ophthalmic solution is administered together with an oral calcium channel blocker or catecholamine-depleting drugs such as reserpine.

Clonidine

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

Epinephrine

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

Quinidine

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

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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

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

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

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

How to Transfer Patients from Other Therapy

When a patient is transferred from another topical ophthalmic beta-adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with pms-TIMOLOL (timolol maleate ophthalmic solution) started on the following day with one drop of 0.25% pms-TIMOLOL ophthalmic solution in the affected eye(s) twice a day. The dose may be increased to one drop of 0.5% pms-TIMOLOL ophthalmic solution twice a day if the clinical response is not adequate.

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

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

Clinical trials have shown the addition of timolol maleate to be useful in patients who respond inadequately to the maximum tolerable antiglaucoma drug therapy.

Missed Dose

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

OVERDOSAGE

There have been report of inadvertent overdosage with timolol maleate ophthalmic solution 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° - 30°C). Protect from light.

The contents of pms-TIMOLOL ophthalmic solution should not be used for more than one month after the date on which the container is first opened.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-TIMOLOL (timolol maleate ophthalmic solution) is supplied as a sterile, isotonic, buffered, aqueous solution. Each mL contains 2.5 mg of timolol (3.4 mg timolol maleate) for 0.25% or 5 mg timolol (6.8 mg of timolol maleate) for 0.5%.

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

pms-TIMOLOL (timolol maleate ophthalmic solution) 0.25% or 0.5% is a clear, colourless to light yellow solution, supplied in a 5 mL or 10 mL fill size in a 11mL white, opaque, plastic ophthalmic dispenser bottle, closed with a white, opaque, plastic dropper and a yellow, opaque, plastic cap with sealing tape.

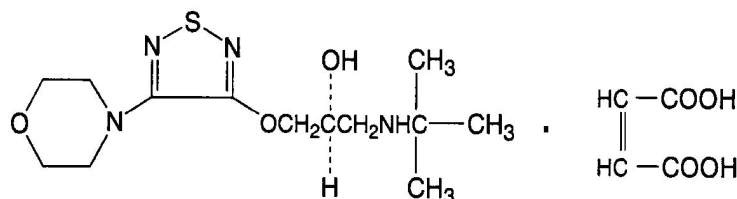
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

| | |
|---------------------------|--|
| Proper name: | timolol maleate |
| Chemical name(s): | (-)-1-(tert-butylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy-2-propanol maleate (1:1) |
| Molecular formula: | C ₁₃ H ₂₄ N ₄ O ₃ S·C ₄ H ₄ O ₄ |
| Molecular mass: | 432.50 |

Structural formula:



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

CLINICAL TRIALS

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

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.

DETAILED PHARMACOLOGY

Timolol maleate reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Onset of action of timolol maleate is usually rapid, occurring approximately 20 minutes after topical application on the eye. Maximum reduction of intraocular pressure occurs in one to two hours. Significant lowering of intraocular pressure has been maintained for as long as 24 hours with 0.25% or 0.5% timolol maleate ophthalmic solution twice 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 topically in studies lasting one and two years respectively.

Acute Toxicity (LD₅₀)

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

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

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

Oral Interactions Studies

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

Subacute Toxicity

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

**pms-TIMOLOL
Timolol Maleate Ophthalmic Solution USP**

This leaflet is part III of a three-part “Product Monograph” published when pms-TIMOLOL (timolol maleate ophthalmic 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 pms-TIMOLOL ophthalmic solution. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

pms-TIMOLOL is the brandname for the medication timolol maleate ophthalmic solution available **only on prescription** through your physician. pms-TIMOLOL (timolol maleate ophthalmic solution) is an ophthalmic solution of a beta-blocking drug which lowers the pressure in the eye for conditions such a 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 conditions.**

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 take pms-TIMOLOL ophthalmic solution if you:

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

What the medicinal ingredient is:

Timolol maleate.

What the important non-medicinal ingredients are:

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

What dosage forms it comes in:

pms-TIMOLOL (timolol maleate ophthalmic solution) is a sterile eye drop.

pms-TIMOLOL (timolol maleate ophthalmic solution) equivalent to 2.5 mg (0.25%) or 5 mg (0.5%) timolol per mL, is a clear to lightly yellow solution supplied in a 5 mL or 10mL fill size in a 11 mL white, opaque, plastic ophthalmic dispenser bottle, closed with a white opaque, plastic dropper and yellow, opaque, plastic cap with sealing tape.

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;
- pms-TIMOLOL (timolol maleate ophthalmic solution) contains benzalkonium chloride as a preservative. This preservative may be absorbed by soft contact lenses. If you wear soft contact lenses, consult your physician before using pms-TIMOLOL ophthalmic solution. Do not administer while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.
- If you have past thyroid problems.
- If you had past eye problems such as choroidal detachment.
- If you had problems or develop problems with blood flow to the brain.
- If you are pregnant or intend to become pregnant.
- If you are breast feeding or intend to breast feed. Timolol has been detected in human breast milk. Discuss with your physician.

pms-TIMOLOL OPHTHALMIC SOLUTION IS NOT RECOMMENDED FOR CHILDREN

INTERACTIONS WITH THIS MEDICATION

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

PROPER USE OF THIS MEDICATION

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

- Do not start taking any other medicines unless you have discussed the matter with your physician or pharmacist.

- If you suspect that pms-TIMOLOL (timolol maleate ophthalmic solution) is causing an allergic reaction (for example, skin rash or redness and itching of the eye), stop its use and contact your physician as soon as possible.
- If you develop any eye irritation or any new eye problems such as redness of the eye or swelling of the eyelids, contact your physician immediately.
- If you are using pms-TIMOLOL ophthalmic solution with another eyedrop, the drops should be instilled at least 10 minutes apart.
- Do not allow the tip of the container to touch the eye or area around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.
- Contact your physician without delay if you have ocular surgery or develop a condition that was not present at the time this medication was prescribed (eg. trauma, an infection, ect.)

Usual Adult dose:

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

The usual dose is one drop in the affected eye(s) in the morning and in the evening.

Overdose:

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

Missed Dose:

It is important to apply pms-TIMOLOL ophthalmic solution 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 medications for the first time, be sure the yellow plastic sealing tape between the bottle and the cap is unbroken (Fig.1).

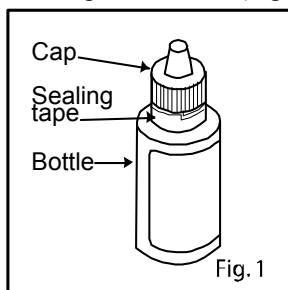


Fig. 1

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

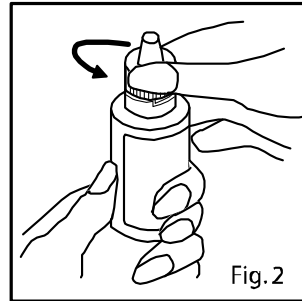


Fig. 2

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

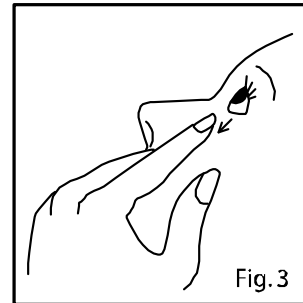


Fig. 3

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

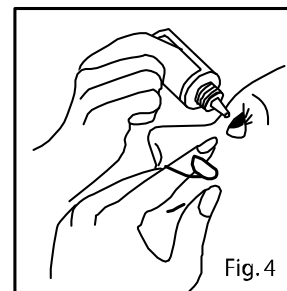


Fig. 4

DO NOT TOUCH YOUR EYE EYELID WITH THE DROPPER TIP.

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

5. Repeat steps 3 & 4 with the other eye if instructed to do

so by your physician.

6. Replace the cap by turning until it is firmly touching the bottle. Do not overtighten the cap.
7. After you have used all doses there will be some pms-TIMOLOL ophthalmic solution left in the bottle. You should not be concerned since an extra amount of pms-TIMOLOL ophthalmic solution has been added and you will get a full amount of pms-TIMOLOL ophthalmic solution that your physician prescribed. Do not attempt to remove excess medicine from the bottle.
8. Tell your physician if you wear contact lenses. Depending on the type of lense, your physician may advise that you re-insert your contact lenses not earlier than 15 minutes after application of pms-TIMOLOL ophthalmic solution.

| | | | | |
|------|---|--|--|---|
| 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 pms-TIMOLOL ophthalmic solution contact your physician or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Any medicine may have unintended or undesirable effects, so-called side effects. Although not all of these side effects may occur, if they do occur, you may need medical attention.
- You may experience eye symptoms such as burning and stinging, dry eyes, redness of the eye, foreign body sensation or visual changes, such as double vision.
- Other side effects may also occur rarely, and some of these may be serious. These may include shortness of breath.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis.
- Your physician or pharmacist has a complete list of the possible side effects from this medication. Please tell your physician or pharmacist promptly about any unusual symptom.
- There are side effects of timolol maleate ophthalmic solution that may affect some patients' ability to drive and use machines.

HOW TO STORE IT

Store at room temperature (15°C -30°C). Protect from light.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Pharmascience Inc. at, 1-888-550-6060.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|--|----------------|--|--------------|--|
| Symptom / effect | | Talk with your physician or pharmacist | | Stop taking the drug and call your physician or pharmacist |
| | | Only if severe | In all cases | |
| Uncommon | Slow heartbeat | | | ✓ |

This leaflet can also be found at:
<http://www.pharmascience.ca>

This leaflet was prepared by
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