Timolol Maleate Ophthalmic Solution, USP 0.25% and 0.5%

COMPARATIVE PRODUCT INFORMATION
# Timolol Maleate Ophthalmic Solution, USP

**Product Information**

**Product:** Timolol Maleate Ophthalmic Solution, USP

**Approval Date:** September 8, 2000

**Indication:** Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

**Description:** Clear, colorless to slightly yellow sterile, isotonic, buffered, aqueous solution in a white, opaque, plastic ophthalmic dispenser bottle, closed with a white, opaque, plastic dropper and white cap.

## Comparative Product Information for Apotex Corp. Timolol Maleate Ophthalmic Solution, USP and Timoptic® 0.25% and 0.5%

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Apotex Corp. Timolol Maleate Ophthalmic Solution, USP 0.25% (% w/v)</th>
<th>Timoptic® a b 0.25% (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timolol Maleate</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Total Phosphatesc</td>
<td>1.85</td>
<td>1.86</td>
</tr>
<tr>
<td>Benzalkonium Chloride</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>To adjust pH</td>
<td>To adjust pH</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Apotex Corp. Timolol Maleate Ophthalmic Solution, USP 0.5% (% w/v)</th>
<th>Timoptic® a b 0.5% (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timolol Maleate</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Total Phosphatesc</td>
<td>1.84</td>
<td>1.78</td>
</tr>
<tr>
<td>Benzalkonium Chloride</td>
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</tr>
</tbody>
</table>

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*a Qualitative ingredient summary to Timoptic® based on April 1995 insert  
b Quantitative ingredient summary for Timoptic® based on the average of three lots  
c Sodium Phosphate Dibasic and Sodium Phosphate Monobasic (on the anhydrous basis) combined
Mechanism of Action

Timolol maleate ophthalmic solution is a nonselective beta-adrenergic receptor blocking agent. Its chemical name is (1R,2R,5S)-1-[(tert-butylation)-3-[4-[morpholin-1-yl]-2, 5-thiadiazol-3-yl]-3-oxopyrrolidine-2-carboxylic acid (timolol maleate). Inactive ingredients: benzalkonium chloride 0.01% or 0.015%, hydroxypropyl methylcellulose 0.4%, sodium chloride 7.5 mg/mL, and propylene glycol 10% solution contains benzalkonium chloride which may be absorbed systemically.

CLINICAL PHARMACOLOGY

Mechanism of Action

Timolol is thought to act by reducing the rate of release of catecholamines from adrenergic nerve terminals. It acts by competing with the sympathetic neurotransmitter norepinephrine for uptake into adrenergic vasoconstrictor nerve endings. In the heart, timolol lowers the rate of both sympathetic and parasympathetic activity. Timolol reduces heart rate, cardiac output, contractility, and systemic vascular resistance. The pharmacodynamic effects of timolol are greatest when the drug is administered to patients with normal sympathetic nervous system tone. In patients with severe autonomic dysregulation or severe hypotension, the extent of the decrease in rate and force of cardiac contraction produced by timolol may be less than expected. The drug generally maintains adequate cardiac performance when used for angina pectoris.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from vasoconstriction of the small arteries and veins of the bronchial circulation. This effect is thought to be responsible for decreased airway responsiveness to exogenous and endogenous bronchoconstrictors. In patients with bronchospastic disease, bronchoconstriction may be mediated both by the sympathetic nervous system and by a reflexive bronchoconstrictor response to hypoxia. Timolol reduces the increased airway responsiveness to exercise, cold air, inhalation of nasal saline, and hyperventilation. It also reverses exercise-induced airway hyperreactivity.

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by a beta-adrenergic receptor blocking agent may precipitate more severe failure. In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, timolol should be discontinued. Patients with chronic obstructive pulmonary disease, sinus bradycardia, or a history of bronchospasm in patients with asthma or rarely death in association with beta-adrenergic blocking agents should be advised to use timolol maleate ophthalmic solution with caution.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, or asthma may use timolol maleate ophthalmic solution with care. However, sufficient doses of epinephrine used to treat anaphylactic reactions. Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be particularly susceptible to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions. Muscle Weakness: Beta-adrenergic blocking agents may be given in combination with other drugs that may lower blood pressure and increase peripheral resistance

PRECAUTIONS

General

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggestive of cerebral vasospasm occur, the blood flow should be maintained. Timolol should be discontinued if no improvement occurs. Timolol is contraindicated in patients with anuria, severe chronic obstructive pulmonary disease, sinus bradycardia; (5) second or third degree atrioventricular block; (6) anuria; (7) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (2) history of bronchial asthma; (3) chronic severe bronchospastic disease, or a history of bronchospastic disease

Muscle Weakness: Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic syndromes. (e.g., myasthenia gravis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients

Patients should be advised to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, 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 solutions. (See PRECAUTIONS, General, Anaphylaxis)

Drug Interactions

Although timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol and epinephrine has been reported. Therefore, timolol should be used with caution in patients subject to spontaneous hypoglycemia or to frequent or accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions. Nitroprusside: Timolol maleate ophthalmic solution contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed before administration of the solution. Lenses may be reinserted 15 minutes following timolol maleate ophthalmic solution administration. Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the risk of hypotension. Beta-adrenergic blocking agents should be administered with caution to patients with peripheral arterial disease. epinephrine, and oral or intravenous calcium antagonists because of possible atropine-like conduction disturbances, left ventricular failure, and hypotension. Timolol should be discontinued in patients administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the risk of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension. Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging the QT interval time.

Quinidine: Potentially systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol. postural hypotension, and inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6. Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, General, Anaphylaxis) Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study of timolol maleate administered orally to rats, there was no statistically significant increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose. In a lifetime oral study in mice, there were statistically significant increases in the incidence of pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended dose.

In a 24-month study in mice, there were statistically significant increases in the incidence of pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended dose.

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Pregnancy:
Reproduction and fertility studies in rats demonstrated no response relationship was observed, and the ratio of test to seven replicate assays), but not in the remaining three strains. Transformation assay (up to 100 mcg/mL). In Ames tests the (doses up to 800 mg/kg) and Timolol maleate was devoid of mutagenic potential when tested with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the micronucleus test and cyogenetic assay (doses up to 800 mcg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/maleate, were associated with statistically significant elevations of reverts observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered a positive test. Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: Teratogenic Effects, Pregnancy Category C. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adverse effects on postnatal development of offspring. Intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day. Dosages above one drop of a 0.5 percent solution twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient’s intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, Drug Interactions, Beta-adrenergic blocking agents.)

OVERDOSAGE

Overdosage has been reported with timolol maleate tablets. A 30 year old female ingested 650 mg of timolol maleate (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered with treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block. An in vitro hemolysis study, using 1C5 timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSEAGE AND ADMINISTRATION

Timolol Maleate Ophthalmic Solution, USP is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent solution in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) twice a day. Since in some patients the pressure-lowering response to timolol may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with timolol.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day. Dosages above one drop of a 0.5 percent solution twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient’s intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, Drug Interactions, Beta-adrenergic blocking agents.)
Timolol Maleate Ophthalmic Solution, USP

STERILE OPHTHALMIC SOLUTION

INSTRUCTIONS FOR USE

Please follow these instructions carefully when using Timolol Maleate Ophthalmic Solution, USP. Use Timolol Maleate Ophthalmic Solution, USP as prescribed by your doctor.

1. If you use other topically applied ophthalmic medications, they should be administered at least 10 minutes before or after Timolol Maleate Ophthalmic Solution, USP.

2. Wash hands before each use.

3. Before using the medication for the first time, be sure the white plastic sealing tape between the bottle and the cap is unbroken (Fig. 1).

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

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

6. 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.

DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.

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

7. Repeat steps 5 & 6 with the other eye if instructed to do so by your doctor.

8. Replace the cap by turning until it is firmly touching the bottle. Do not overtighten the cap.

9. The dispenser tip is designed to provide a pre-measured drop; therefore, do NOT enlarge the hole of the dispenser tip.

10. After you have used all doses, there will be some Timolol Maleate Ophthalmic Solution, USP left in the bottle. You should not be concerned since an extra amount of Timolol Maleate Ophthalmic Solution, USP has been added and you will get the full amount of Timolol Maleate Ophthalmic Solution, USP that your doctor prescribed. Do not attempt to remove excess medicine from the bottle.

WARNING: Keep out of reach of children.

If you have any questions about the use of Timolol Maleate Ophthalmic Solution, USP, please consult your doctor.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL 33326

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