

## PHYSICIANS CIRCULAR

Ophthalmic Solution  
**TIMOPTOL**<sup>®</sup>  
(timolol maleate, MSD)

TIMOPTOL\* (timolol maleate, MSD) 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. TIMOPTOL is available with or without preservative, benzalkonium chloride.

Onset of action of TIMOPTOL is usually rapid, occurring approximately 20 minutes after topical application to 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 percent or 0.5 percent Ophthalmic Solution TIMOPTOL. This extended duration of action permits control of intraocular pressure over the usual sleeping hours. Repeated observations over a period of three years indicate that the intraocular pressure-lowering effect of TIMOPTOL is well maintained.

Timolol maleate is a nonselective  $\beta$ -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 TIMOPTOL in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Unlike miotics, TIMOPTOL 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 TIMOPTOL a refraction might be necessary when these effects of the miotic have passed.

In clinical studies TIMOPTOL was generally effective in more patients and produced fewer and less severe side effects than either pilocarpine or epinephrine.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTOL after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

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

---

\* Trademark of MERCK & CO., Inc., Whitehouse Station, NJ, USA

## INDICATIONS

TIMOPTOL is indicated for the reduction of elevated intraocular pressure.

In clinical trials it has been shown to reduce intraocular pressure in:

- Patients with ocular hypertension
- Patients with chronic open-angle glaucoma
- Aphakic patients with glaucoma
- Some patients with secondary glaucoma
- 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 PRECAUTIONS)

TIMOPTOL is also indicated as concomitant therapy in patients with pediatric glaucoma, who are inadequately controlled with other antiglaucoma therapy.

## DOSAGE AND ADMINISTRATION

The usual starting dose is one drop of 0.25 percent TIMOPTOL 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.

For a small proportion of patients one drop of 0.1 percent TIMOPTOL in the affected eye(s) twice a day may be satisfactory. If the clinical response is not adequate with 0.1 percent solution, the dosage should be increased to one drop of 0.25 percent in the affected eye(s) twice a day.

If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with TIMOPTOL. The use of two topical beta-adrenergic blocking agents is not recommended (see PRECAUTIONS).

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

If the intraocular pressure is maintained at satisfactory levels, many patients can be placed on once-a-day therapy.

### 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 TIMOPTOL started on the following day with one drop of 0.25 percent TIMOPTOL in the affected eye twice a day. The dose may be increased to one drop of 0.5 percent TIMOPTOL 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 percent TIMOPTOL in each affected eye twice a day. On the following day, discontinue the previously used

antiglaucoma agent completely and continue with TIMOPTOL. If a higher dosage of TIMOPTOL is required, substitute one drop of 0.5 percent solution in each affected eye twice a day.

### USE IN CHILDREN

The usual starting dose is one drop of 0.25 percent TIMOPTOL in the affected eye(s) every 12 hours, in addition to other antiglaucoma medication. The dosage may be increased to one drop of 0.5 percent solution in the affected eye(s) every 12 hours, if necessary. The use of TIMOPTOL is not recommended in premature infants or neonates.

### PRESERVATIVE-FREE UNIT DOSE

For patients who may be sensitive to the preservative benzalkonium chloride, or when use of a preservative-free topical medication is advisable, a formulation of TIMOPTOL without the preservative benzalkonium chloride is available. This formulation is packaged in individual unit dose containers of two strengths: 0.25% or 0.5%.

Preservative-Free Unit Dose TIMOPTOL is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be maintained after the individual unit is opened, the remaining contents should be discarded immediately after administration.

## **CONTRAINDICATIONS**

TIMOPTOL is contraindicated in patients with:

- Bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- Sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure; cardiogenic shock
- Hypersensitivity to any component of this product

## **PRECAUTIONS**

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of  $\beta$ -adrenergic blocking agents may occur with topical administration.

Cardiac failure should be adequately controlled before beginning therapy with TIMOPTOL. 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 TIMOPTOL.

Patients who are already receiving a  $\beta$ -adrenergic blocking agent systemically and who are given TIMOPTOL should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of  $\beta$ -blockade. The use of two topical  $\beta$ -adrenergic blocking agents is not recommended.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTOL has little or no effect on the pupil. When TIMOPTOL is used to reduce elevated intraocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

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

TIMOPTOL contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Therefore, TIMOPTOL 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.

#### 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. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

#### DRUG INTERACTIONS

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

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.

The potential exists for additive effects and production of hypotension and/or marked bradycardia when TIMOPTOL is administered together with an oral calcium entry blocker, catecholamine-depleting drugs or  $\beta$ -adrenergic blocking agents.

Oral  $\beta$ -adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

#### USE IN PREGNANCY

TIMOPTOL has not been studied in human pregnancy. The use of TIMOPTOL requires that the anticipated benefit be weighed against possible hazards.

#### NURSING MOTHERS

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from TIMOPTOL in 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.

### **SIDE EFFECTS**

TIMOPTOL 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.

#### 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, choroidal detachment following filtration surgery (see PRECAUTIONS), tinnitus.

#### Cardiovascular

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, congestive heart failure, palpitation, cardiac arrest, edema, claudication, Raynaud's phenomenon, cold hands and feet.

#### Respiratory

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

#### Body as a Whole

Headache, asthenia, fatigue, chest pain.

#### Integumentary

Alopecia, psoriasiform rash or exacerbation of psoriasis.

#### Hypersensitivity

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

#### Nervous System/Psychiatric

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

#### Digestive

Nausea, diarrhea, dyspepsia, dry mouth.

#### Urogenital

Decreased libido, Peyronie's disease.

#### Immunologic

Systemic lupus erythematosus.

#### Potential Side Effects

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

### **OVERDOSAGE**

There have been reports of inadvertent overdosage with TIMOPTOL 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 SIDE EFFECTS).

### **AVAILABILITY**

TIMOPTOL  
(timolol maleate, MSD)

PAK-TOT-OS-112005

TIMOPTOL<sup>®</sup> (timolol maleate, MSD) is available in the strength of 0.25% and 0.5 %, Both are available in 3ml vial.

#### STORAGE

TIMOPTOL is a clear, colorless to light yellow solution.  
TIMOPTOL is stable at room temperature. Protect from light.